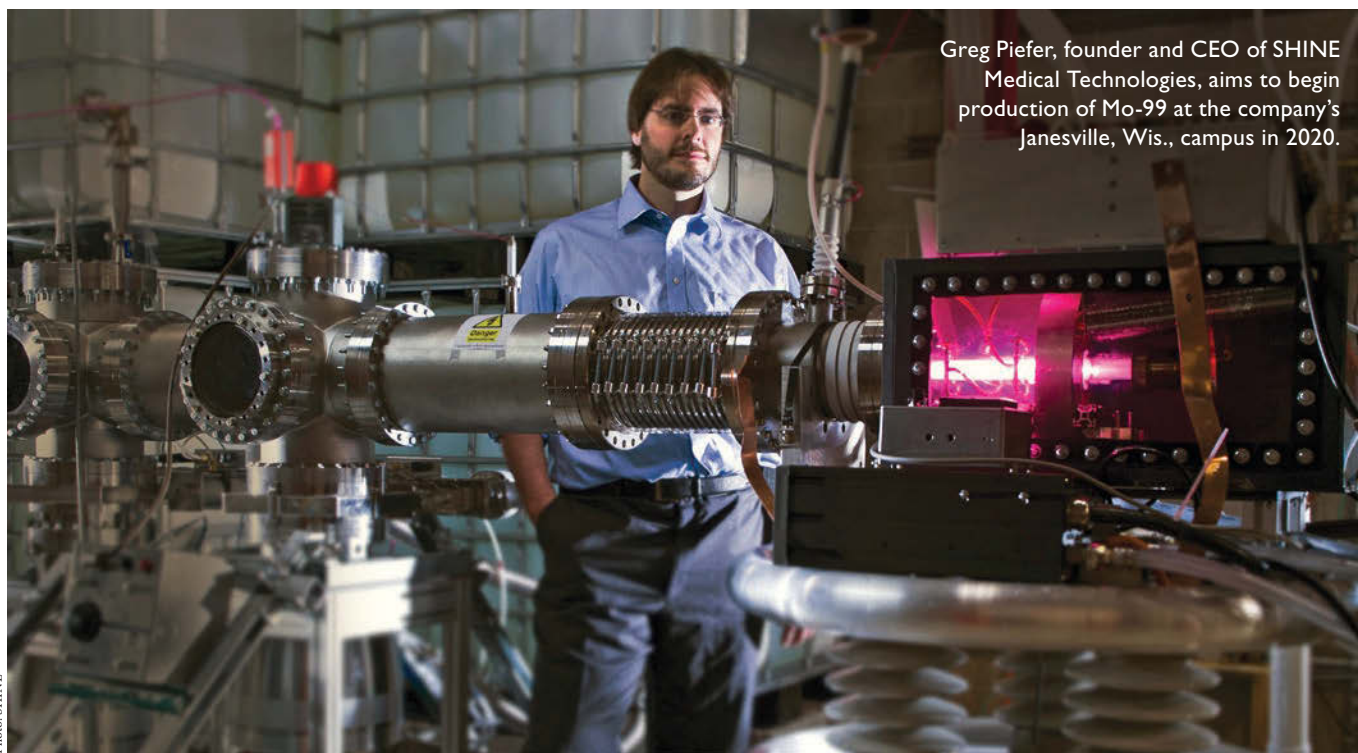


Greg Piefer, founder and CEO of SHINE Medical Technologies, aims to begin production of Mo-99 at the company's Janesville, Wis., campus in 2020.

Photo: SHINE



## Meeting the moly-99 challenge

*In the race to create a stable supply of the important medical radioisotope molybdenum-99, several private companies are leading the way.*

By Tim Gregoire

On April 2, Canadian Nuclear Laboratories announced on its Facebook page that the National Research Universal (NRU) reactor at Canada's Chalk River Laboratories "quietly shut down for the last time" on March 31. The NRU once accounted for about 40 percent of the world's supply of the radioisotope molybdenum-99. The majority of Mo-99 is now produced by research reactors in Australia, Europe, South Africa, and Russia, many of them in use since the 1960s.

After Canadian Nuclear Laboratories announced in 2000 that Mo-99 production would eventually cease at NRU, it became clear that the world's supply of this important medical isotope was in jeopardy. This concern was heightened after a number of Mo-99-producing reactors coincidentally experienced unplanned shut-downs, including the NRU reactor in 2007 and the High Flux Reactor at Petten in the Netherlands and the reactor at Belgium's Institute of Radioelements in 2008.

As governments realized that maintaining the availability of Mo-99 relied on a few aging reactors whose future was

uncertain, they began looking at options for maintaining a reliable source of the isotope. In the United States, the American Medical Isotope Production Act of 2012 was passed in an effort to establish a technology-neutral program to support the domestic production of Mo-99 for medical uses by private entities. The bill also sought to phase out the export of high-enriched uranium for the production of medical isotopes over a period of seven years.

It is estimated that Mo-99 is used in about 50,000 medical procedures in the United States each day. Mo-99 decays into technetium-99m, which is often referred to as the workhorse isotope of nuclear medicine for diagnostic imaging. Tc-99m has a half-life of about six hours and emits 140 keV photons when it decays to Tc-99, a radioactive isotope with about a 214,000-year half-life. The gamma decay of Tc-99m makes it useful for diagnostic imaging, where pharmaceutical compounds containing the isotope are injected into the body and traced through the use of gamma cameras to help diagnose heart disease and cancer, to study organ structure and function, and to perform other important medical applications.

Because of its relatively short half-life of 66 hours, Mo-99 cannot be stockpiled and must be made on a continuous basis to ensure its availability. As noted by the National Academy of Sciences, the processes for producing Mo-99 and Tc-99m generators and delivering them to customers are tightly scheduled and highly time dependent. An interruption at any point in the production or transportation operation can have substantial impacts on patient care.

Since 2009, the Department of Energy, through the National Nuclear Security Administration, has led a program aimed at accelerating the commercial production of Mo-99 in the United States without the use of HEU. The goal of the NNSA's Mo-99 program is twofold: to establish a reliable supply of the isotope and at the same time eliminate the use of HEU in accordance with U.S. nuclear nonproliferation policies. According to the NNSA, creating a commercial Mo-99 supply network that avoids a single point of failure and that does not use HEU requires cooperation and coordination among government, industry, and the medical community. To help fund commercial projects, the NNSA has used cooperative agreements that pro-



Photo: SHINE

In February, SHINE completed the construction of Building One, the first building of its new medical isotope campus.

vide up to \$25 million in matching funds, based on a 50-50 cost-share between the NNSA and its commercial partners.

Following a technology-neutral approach, the NNSA currently has cooperative agreements with three partners for four projects: NorthStar Medical Radioisotopes, General Atomics, and SHINE Medical Technologies. According to the NNSA, the program's approach recognizes that success is more likely to be found through the parallel development of several production technologies.

### The SHINE approach

With a current staff of about 70, a modern office in downtown Janesville, Wis., and a new production campus under construction nearby, SHINE Medical Technologies is one of the leading contenders in the race to be a large-scale global supplier of Mo-99. SHINE's system uses a low-energy, accelerator-based neutron source and a low-enriched uranium (19.75 percent U-235) aqueous target solution to produce Mo-99. The particle accelerator generates neutrons by colliding deuterium ions into a tritium gas, causing a fusion of the hydrogen isotopes. In a noncritical fission reaction, the resulting neutrons are injected into the LEU target solution.

"From our standpoint, the elimination of the nuclear reactor as the primary source of neutrons has massive benefits," said Greg Piefer, founder and chief executive officer of SHINE. Piefer noted that most current Mo-99 production methods need a nuclear reactor operating at criticality to irradiate a solid LEU target, and those reactors are expensive to build and maintain. "Reactors have a cost factor associated with them both in terms of capital cost and ongoing operating costs, which is something that we would rather live without," he said.

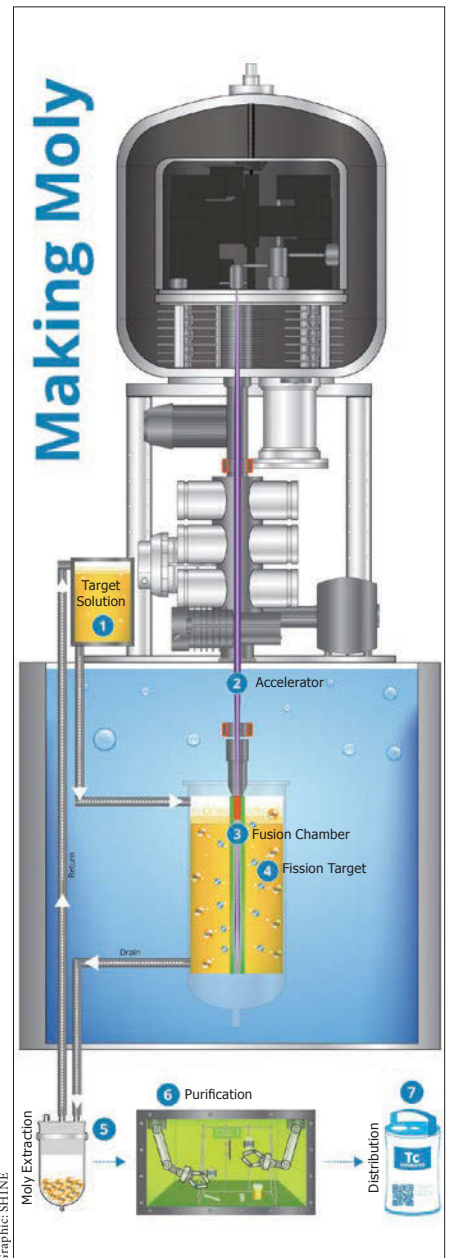
Piefer also said that the use of an aqueous target has additional benefits as opposed to the use of conventional targets of

solid LEU or HEU plates or foils, a process that he called cumbersome and wasteful. "The aqueous target allows us to do a couple of things that are really nice," he said. "First, it allows for massively simpler processing. We don't have to pack our target up, and we don't have to have human beings engaged with it while it's moving to the processing facility. Our processing facility is collocated in the same building as our irradiation facility."

Rather than shipping irradiated targets from a reactor to a separate facility for processing and Mo-99 capture, the SHINE system will pump the liquid LEU target from the accelerator tank to hot cells and extraction columns that use titanium to pull the Mo-99 from the solution. The target solution can then be returned to the accelerator for further irradiation.

In addition to the cost and dose savings of having the irradiation and extraction processes collocated, Piefer noted that the SHINE process generates less waste than conventional fission-based systems. Other than generating some low-level activation in the accelerator structure and components, the system produces some fission products in the target solution, about 20 percent of which can be commercialized, he said. The remaining products will be disposed of as low-level radioactive waste. Piefer further noted that the target solution will be recycled and reused for several years, allowing for the short-lived products to decay away. Once the target solution can no longer be used, it will be grouted, allowed to cool, and then disposed of at a commercial low-level waste facility.

Piefer said that once commercial production starts, which is planned for the second half of 2020, SHINE will be the largest single Mo-99 producer in the world. Initially, SHINE expects to produce around 4,000 six-day curies per week. SHINE's operating license, however, is based on producing 8,000 six-day curies per week, Piefer said, adding that the com-



Graphic: SHINE

SHINE's accelerator-based system uses an aqueous LEU target at noncritical rates to produce Mo-99.

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pany will be able to continually increase production if the demand exists. A six-day curie is defined as the amount of Mo-99 activity that is left six days after it leaves production.

“The market is growing,” Piefer said. “I would say that by 2025, this facility should be able to provide about 40 to 50 percent of global demand, probably maintaining close to 50 percent.” At full operations, SHINE will have a staff of around 150 to 170, Piefer said.

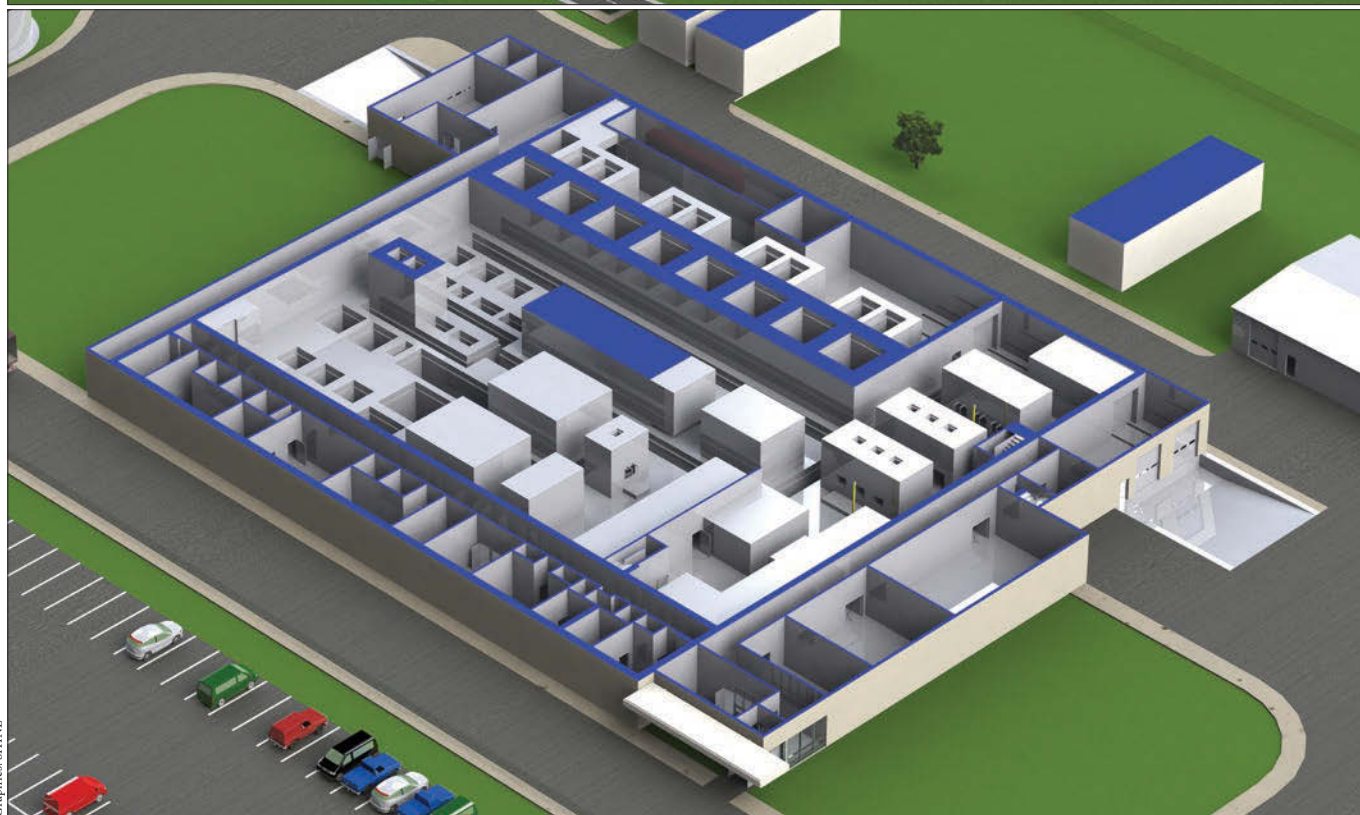
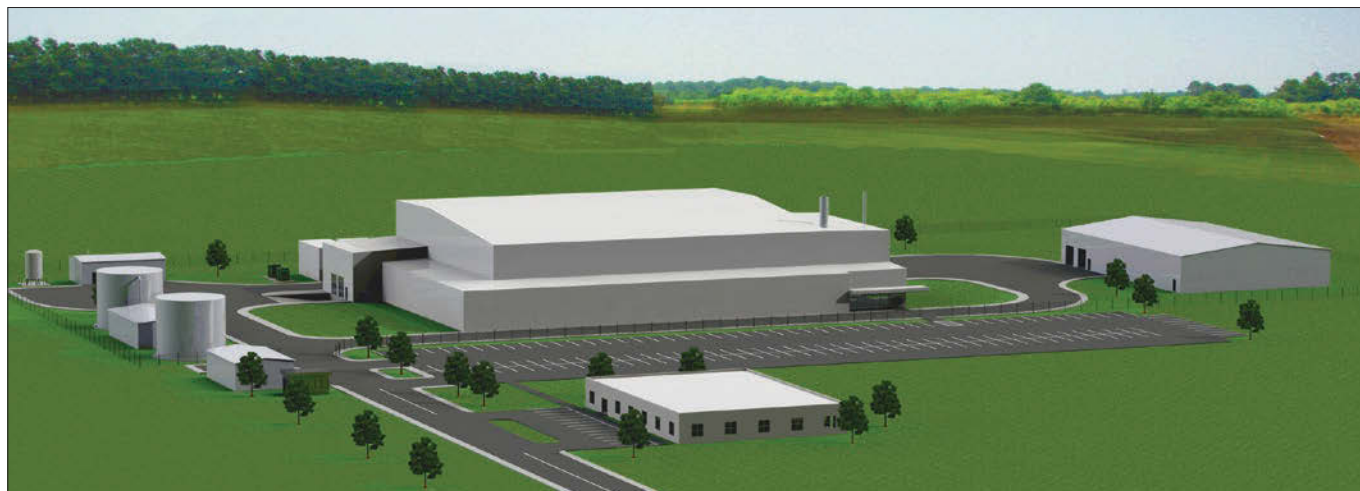
In February, SHINE completed the construction of the first building, Building One, on the company’s planned campus on the south side of Janesville. Building One will be used to house SHINE’s first integrated, full-size production system. During the construction of the

main production facility, scheduled to begin later this year, Building One will be used to develop an operating history with equipment, during which testing will be done and lessons gathered. “We are very confident that we have proved the technology already in terms of neutron yield and accelerator performance, as well as the performance of the liquid target at scale,” Piefer said. “But what we haven’t done is prove the production equipment itself.”

The next critical milestone on the path to commercial production for SHINE is receiving its operating license from the Nuclear Regulatory Commission. Piefer said that currently the company is in “a full-fledged, full-bore effort” to finalize its operating license application, with plans

to submit it to the NRC later this year. Per the NRC’s guidance, SHINE is planning on an 18–24 month review process for the application, with the hope of receiving license approval in 2020, in line with its production goals.

As a partner in the NNSA’s Mo-99 program, SHINE has received the full \$25 million in DOE matching funds. Piefer said that equates to about 10 percent of the total cost of commercializing its production technology. While the company has received some assistance from state and local sources, Piefer said that the majority of its funding is from private investments. “We have a wide range of investors, from local people here in Janesville who just like the SHINE story, up to angel investors,” he said.



**Top:** SHINE’s main production facility, seen here in a computer rendering, will be capable of producing up to 8,000 six-day curies of Mo-99 a week, according to the company. **Bottom:** The interior of SHINE’s main production facility is shown in this cutaway rendering.

Graphics: SHINE

### Other runners

SHINE is not the only company making real progress in pursuing commercial Mo-99 production using LEU. About 13 miles south of Janesville, in Beloit, Wis., NorthStar Medical Radioisotopes, another partner in the NNSA's Mo-99 program, is pursuing a non-uranium production system using naturally occurring molybdenum. In February, the U.S. Food and Drug Administration approved NorthStar's Tc-99m generator, the RadioGenix System (NN, Mar. 2018, p. 94).

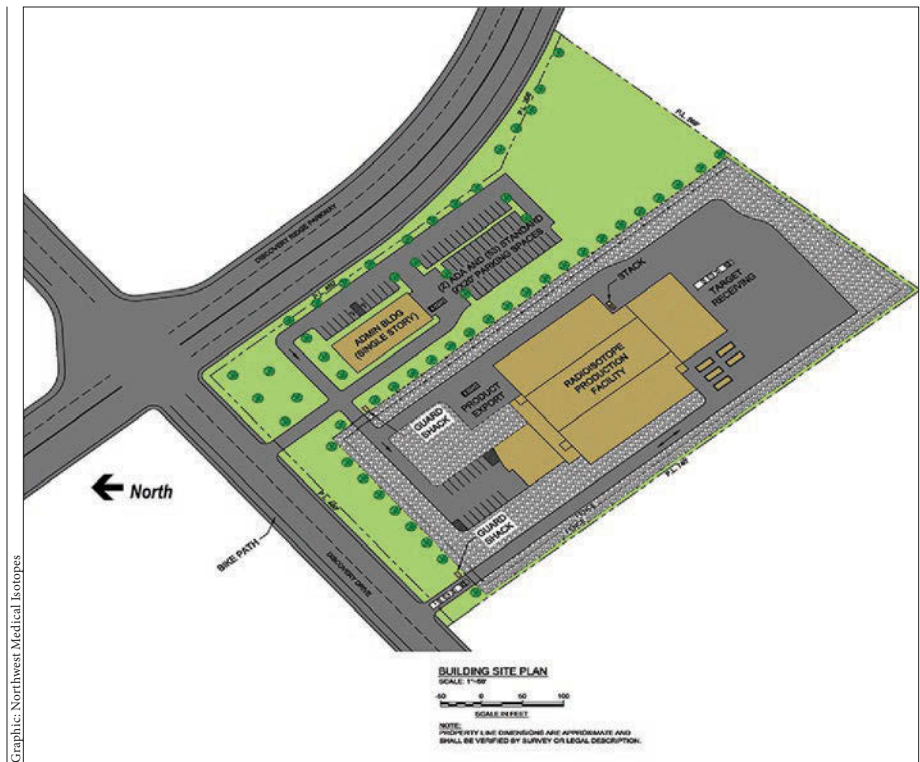
According to NorthStar, its processes are based on proven, well-established principles yet mark a significant technological advancement over current technology. The company's production process involves the use of solid targets of natural Mo, containing about 24 percent Mo-98, which are irradiated at the University of Missouri Research Reactor (MURR) in Columbia, Mo., to produce Mo-99 through neutron capture. The irradiated targets are then dissolved and placed in source vessels, which upon arrival at the radiopharmacy are mounted into the RadioGenix System to extract the Tc-99m.

NorthStar said that it expects to have the capability to supply up to 10 percent of U.S. Mo-99 demand by the end of 2018 and is planning to scale up production to increase capacity over the coming years. In



Photo: NorthStar Medical Radioisotopes

The RadioGenix System Tc-99m generator from NorthStar Medical Radioisotopes was approved by the FDA in February.



In May, Northwest Medical Isotopes received approval from the NRC to construct a radioisotope production facility at the Discovery Ridge Research Park in Columbia, Mo.

a process akin to learning to crawl, walk, and then run, NorthStar will increase production through two additional development phases. In the next phase, the company will increase Mo-99 yield through the neutron capture of enriched Mo-98 (about 95 percent Mo-98). In the third phase, NorthStar will employ an electron accelerator to induce photo transmutation (neutron knock-out) of enriched Mo-100.

The company said that it is well advanced with its enriched Mo-98 program and expects to submit an application for regulatory approval late this year or in early 2019, with FDA approval of the enriched target material expected in the second half of 2019. Having established proof of concept of its accelerator program, NorthStar currently is focused on the completion of its Beloit production facility, with the installation of the accelerators expected in 2019 or 2020.

Other companies outside of the NNSA Mo-99 program are also making progress. On May 3, the NRC commissioners authorized the agency's Office of Nuclear Reactor Regulation to issue a construction permit to Northwest Medical Isotopes (NWMI) for a Mo-99 production facility at the Discovery Ridge Research Park in Columbia, Mo.

According to the NRC, NWMI would fabricate LEU targets for irradiation at MURR, the Oregon State University TRIGA reactor, or a third, as yet unidentified, reactor. The targets then would be shipped back to NWMI's planned production facility in Columbia for the recovery

and purification of Mo-99.

On May 7, Lynchburg, Va.-based BWX Technologies (BWXT) announced that it has developed its own Mo-99 manufacturing process. Similar to the NorthStar process, BWXT will use natural Mo rather than LEU targets to produce Mo-99 through a patent-pending neutron capture process. The Mo-99 produced will be used in Tc-99m generators that are in commercial development at BWXT.

BWXT said that it anticipates entering the roughly \$400-million global Tc-99m segment through generator sales to radiopharmacies, with an initial focus on North America. The company expects to submit its line of Tc-99m generators for regulatory approval in 2019. In addition, BWXT plans to introduce the Mo-99 product line by the end of 2019, subject to regulatory approvals.

Outside of the United States, the Australian government issued an operating license to the Australian Nuclear Science and Technology Organization (ANSTO) in April for its Mo-99 production facility (see Isotopes & Radiation, p. 29). The ANSTO nuclear medicine facility will extract and purify Mo-99 from LEU plates irradiated in Australia's OPAL reactor.

Judging from the companies themselves, it would appear that a steady, reliable supply of Mo-99 is only a few years, if not months, away. Whether the private enterprises will be able to meet their self-imposed schedules or scale up their operations as intended, however, remains to be seen. **NW**