Actinium-225 Production and the Future Needs for Labeled Drugs

By Dr. Richard Zimmermann

As the R&D and the clinical interest for Actinium-225 labeled molecules increases, questions regarding future availability of industrial-scale quantities of this isotope cast doubt on the marketing viability of ^{225}Ac-labeled drugs. In a recent publication entitled 'Is Actinium Really Happening', the short editorial concludes with an obvious answer "yes, of course excess actinium will be available", however adds a "but" announcing the limit of the success.

The paper emphasizes that, within the next 10 years, an important number of stakeholders will invest substantial sums to expand industrial capacity access to ^{225}Ac for the high number of ^{225}Ac-labeled drugs that are currently under development. More than a dozen of these molecules have already been injected in man and the first of them could reach the market by 2028, coinciding with increased access to high-quality radionuclides produced under Good Manufacturing Practices (GMP). In the following years, the worldwide capacity will even exceed needs, probably resulting in an interesting price competition benefiting the patients. Non-carrier-added quality ^{225}Ac, meaning in this case, ^{225}Ac without ^{227}Ac contamination, will be used exclusively in human. As a consequence of higher yields, the technologies based on accelerators (cyclotrons, linacs, rhodotrons) will remain the only profitable tools, while the presently generator-based production will stay in use until larger amounts of ^{225}Ac can be produced with the newest technologies.

The journey towards the first marketed ^{225}Ac-drug still requires some patience given the time required to develop new tools (2 to 5 years) and source the requisite material, Radium-226, which is common across all production technologies. Encouragingly, almost all players are slowly finding addressing this challenge, which should be resolved within the next three years. As a reminder, the industrial production of ^{226}Ra was stopped in 1954, but during this year more than 2.3 kg of this material was extracted and purified, underscoring the importance of investment priorities and political will.

Next to solving the access to ^{226}Ra, engineers will have to make sure that the risk of explosion of the targets in these new high-capacity production tools remains close to zero as, with the long half-life of the target material, any accident in such site could lead to a shut-down of the center for hundreds of years and jeopardize the other sites. However, the major issue that needs to be anticipated is rather a political issue and not specific to ^{225}Ac, but applicable for all long half-life radionuclides. As the pharmaceutical industry is aiming at treating several hundreds of thousands of patients a year which translates into millions of doses, a concern will be addressed by green groups looking at preserving the planet and in particular water systems if no action is taken to control the waste generated by the patients that are being treated. Ambulatory treatment can work as long as only a few thousands of patients are being treated, but by 2032, the industry, the hospitals and the authorities will have to propose a solution to minimize the risk of river pollution. There remains no risk for patients or for the population.

With this last point in mind, looking ahead, Actinium-225 (as well as Lutetium-177) holds promise but within a limited timeframe. All the molecules that have entered or are close to entering clinical trials within the next two years stand a high chance of becoming blockbusters. However, if molecules labeled with radioisotopes with shorter half-lives (e.g., labeled with ^{211}At or ^{212}Pb) reach the market in a form that is readily available and demonstrates the same efficacy; it can easily displace the equivalent long half-life radiolabelled molecules.

Short half-life radionuclides will bear a strong ecological marketing advantage which may lead to a switch even before 2035 and lasting over a 10 to 15 years period. While we embrace the decade of ^{225}Ac ,it is now time to prepare for the next generation of radiotheranostics.

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