

Improving access to innovative radiopharmaceuticals in China

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Executive Summary

Radiopharmaceuticals are unique medicines that use particles or rays emitted by radioisotopes for both diagnosis and treatment. Radiopharmaceuticals are fundamental elements of nuclear medicine. They serve as the foundation of molecular imaging and precision medicine and contribute to novel approaches in the early diagnosis and precision treatment of diseases. Innovative radiopharmaceuticals are bio-targeted therapies that are composed of a targeting molecule (ligand) attached to a therapeutic radioisotope. The ligand delivers radioisotopes that directly target lesions. Then radioisotopes emit ionizing radiation to kill diseased cells, with minimal impact to healthy tissues. Innovative radiopharmaceuticals have shown the potential to change patients' outlook on diagnosis and treatment of cancer, cardiovascular diseases, and neurodegenerative disorders.

Over the past several decades, China has made significant progress in the research, development, and clinical application of radiopharmaceuticals. This said, there remains significant growth potential for China's radiopharmaceutical industry.

This report outlines some important benefits of radiopharmaceutical therapy and identifies opportunities to address the challenges to the development of the radiopharmaceuticals industry in China. With the implementation of the *Healthy China 2030 Initiative*, and the Chinese radiopharmaceutical industry under development, the coming years represent a critical period and opportunity for China to overcome these challenges. To help patients obtain and benefit from radiopharmaceutical treatment, it will be important for all stakeholders to partner in the development of a sustainable ecosystem to better support the radiopharmaceutical industry in China.

As a government-supported strategic emerging industry, nuclear medicine is becoming an important industry that will contribute to the high-quality development of medical and healthcare in China. Issued in 2021, *The Medium and*

Long-Term Development Plan (2021-2035) for Medical Isotopes establishes an overall framework from within China may develop the radiopharmaceutical industry. To help ensure that this advanced treatment can better reach Chinese patients, Novartis encourages the Chinese government to consider the following key areas:

- **Optimize regulatory frameworks and policies.** Propose strengthening the cross-departmental regulatory coordination system for radiopharmaceuticals and to conduct scientific supervision while balancing its unique property of being both a medicine and having radioactivity. Establish a relevant technical evaluation system that meets the characteristics of radiopharmaceuticals and ensures practical and relevant radiation and environmental protection policies, thereby appropriately and scientifically relaxing restrictions on new therapeutic nuclides.
- **Support the construction and development of nuclear medicine departments.** Optimize the licensing application procedure for the clinical use of radiopharmaceuticals in hospitals and increase the quotas for medical isotopes in medical institutions; offer necessary assistance and guidance for hospitals and healthcare personnel (including hardware facilities and trainings, etc.); establish relevant standards for the clinical use of radiopharmaceuticals and enhance radiation safety management.
- **Further improve patient access to medicines.** Establish a national or regional comprehensive pricing model and charging basis that is more standardized and in line with the actual diagnosis, treatment technology and labor costs. Promote the increased inclusion of innovative radiopharmaceuticals for inclusion in the NRDL and explore the establishment of a classification system for therapeutic radiopharmaceuticals based upon the existing NRDL diagnostic radiopharmaceutical classification system.

Novartis is committed to supporting the Chinese government's efforts to address current and new healthcare challenges and to meet the people's health needs via continuous medical innovation.

Preface

Over the past few decades, significant progress in cancer treatment has been made. This said, effective treatment options for patients remain limited, particularly for patients who suffer from rare, resistant, or metastatic cancer.¹ New treatments are needed to improve both survival and quality of life.² As the second leading cause of death globally,³ cancer has become a major global public health and economic challenge.

With the continuous innovation in biomedicine, innovative radiopharmaceuticals offer an effective therapeutic approach for patients with limited treatment options. Radiopharmaceuticals are a class of drugs that consist of radionuclides that can be used for diagnostic or therapeutic purposes. In recent years, tremendous progress has been made in the development of radioligand therapies and innovative radiopharmaceuticals. They play an irreplaceable role in personalized and targeted treatment against a small number of cancers and offer a promising approach to treat broader cancer and non-cancer conditions.⁴

Over the past six decades, China has made steady advances in the research, development, and application of radiopharmaceuticals. Through the adoption of several national policies, the China radiopharmaceutical industry in China has continued to grow.⁵ Compared with Europe and the United States, however, a large gap remains regarding the types of medical radionuclides and radiopharmaceuticals that have been granted marketing approval in China. This may be attributed to some degree to the radiopharmaceutical regulatory frameworks and policies, the inadequate establishment and development of nuclear medicine departments, and the need to improve patient access to these medicines.

To accelerate the improvement of national health policy and to continuously meet growing healthcare needs, the General Office of the State Council issued the *14th Five-Year Plan for National Health* and formulated corresponding development

¹ Rahbar K, Bode A, Weckesser M, et al. 2016. Radioligand Therapy With ¹⁷⁷Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med* 41(7):522-8

² Khan S, Krenning EP, van Essen M, et al. 2011. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [¹⁷⁷Lu-DOTA0,Tyr3]octreotate. *J Nucl Med* 52(9): 1361-8

³ World Health Organization. 2018. Cancer. https://www.who.int/health-topics/cancer#tab=tab_1

⁴ The Health Policy Partnership. Radioligand therapy realizing the potential of targeted cancer care. <https://www.healthsystemreadiness.com/app/uploads/2021/05/Radioligand-therapy-realising-the-potential-of-targeted-cancer-care.pdf>

⁵ HU Ji, LI Hongyu, SUI Yanying, et al. Current status and future perspective of radiopharmaceuticals in China. *Eur J Nucl Med Mol Imaging* 49, 2514-2530 (2022)

indicators.⁶ The report of 20th CPC National Congress⁷ highlighted the importance of prioritizing and ensuring people's health. Supporting the development of the nuclear medical industry as a strategic emerging industry,⁸ and promoting the development of innovative radiopharmaceuticals can and should be of strategic importance for promoting the high-quality development of China's medical and health undertakings and supporting the construction of Healthy China.

It is important that action be taken to help ensure China cancer patients have access to these effective life-saving treatments when they need it.

Situational analysis and Novartis recommendations

Cancer incidence and deaths in China continue to rise, and the overall cancer burden in China continues to increase.⁹ According to data released by the International Agency for Research on Cancer of World Health Organization, China had 4.57 million new cancer cases and 3 million deaths in 2020, both of which rank first in the world.¹⁰

Radiopharmaceuticals are a class of drugs that contain radionuclides, primarily used for diagnostic and therapeutic purposes, with the former dominating the market.¹¹ Radiopharmaceuticals are widely used to diagnose and treat cancer, myocardial imaging, diagnosis of heart disease, and status monitoring of neurodegenerative diseases. Its clinical application has become a safe and effective frontier treatment method, providing a new means and more effective way for early diagnosis and timely treatment.¹²

Radioligand therapy is an innovative type of targeted therapy based on radiopharmaceuticals. It uses radionuclides to selectively target and treat diseased tissues. This represents a revolutionary means to accurately diagnose and treat

⁶ State Council. National Health Plan for the 14th Five-Year Plan. http://www.gov.cn/zhengce/content/2022-05/20/content_5691424.htm

⁷ The report of 20th CPC National Congress. http://www.gov.cn/xinwen/2022-10/25/content_5721685.htm

⁸ State Council. Circular of the State Council on National Strategic Emerging Industry Development Plan for the 13th Five-Year Plan. http://www.gov.cn/zhengce/content/2016-12/19/content_5150090.htm

⁹ Rongshou Zheng, Siwei Zhang, Hongmei Zeng, et al. Cancer incidence and mortality in China, 2016. *Journal of the National Cancer Center*, 2022, 2(1):1-9

¹⁰ International Agency for Research on Cancer of World Health Organization. GLOBOCAN 2020, <http://gco.iarc.fr/today>

¹¹ LI Jianguo, QIN Xiujun, HU Bo, et al. Research Status and Prospect of Radiopharmaceuticals. *Chinese Journal of Pharmacovigilance*, 2019,16(1):27-31

¹² Czarniecki M, Mena E, Lindenberg L, et al. Keeping up with the prostate-specific membrane antigens (PSMAs): an introduction to a new class of positron emission tomography (PET) imaging agents[J]. *Translational Andrology and Urology*, 2018, 7 (5):831-843

malignant tumors.¹³ This treatment delivers radionuclides or radionuclide-labeled drugs to target diseased tissues or cells. Radionuclides are concentrated in the targeted tissues and use the biological effects of ionizing radiation emitted by radionuclides to inhibit or kill the diseased cells, while inflicting relatively light damage to the surrounding normal and healthier tissues.¹⁴ Radioligand therapy has brought positive treatment benefits for patients with neuroendocrine tumors and prostate cancer. It is likely that additional therapeutic radiopharmaceuticals will be introduced for patients suffering from other cancer types, including advanced stage of breast, kidney, colon, and pancreatic cancer, and perhaps other tumor types.¹⁵ In recent years, therapeutic radiopharmaceuticals are increasingly receiving wide attention due to the treatment options offered to patients and healthcare providers, but also due to the economic benefits and market potential.

China's nuclear medicine programs can be traced back to 1956.¹⁶ With the rapid development of China's national economy, China's market for radiopharmaceuticals has also grown. In addition to traditional radiopharmaceutical companies, new enterprises are being created and collectively they are contributing to the development of the radiopharmaceutical field and the radiopharmaceutical industry in China. The value of the radiopharmaceuticals market is also becoming increasingly prominent. According to Frost & Sullivan, the compounded annual growth rate of the radiopharmaceuticals market in China is second to that of biological drugs, and it is estimated that the market size of radiopharmaceuticals will reach US\$ 1.14 billion by 2023.¹⁷

Despite the significant progress that has been made in China's radiopharmaceutical research, development and application over the past 60 years, China's radiopharmaceutical industry remains comparatively less developed compared to that of the United States and European countries. This is particularly true in the area of therapeutic radiopharmaceuticals.⁵ While the global radiopharmaceutical market reached US\$5.9 billion in 2020, the China market contributed approximately 8% of the global market, or roughly US \$472 million.¹⁸ Annually, there are more than 20

¹³ Hofman MS, Violet J, Hicks RJ, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study [J]. *Lancet Oncology*, 2018, 19(6): 825-833

¹⁴ Virgolini I, Decristoforo C, Haug A, et al. 2018. Current status of theranostics in prostate cancer. *Eur J Nucl Med Mol Imaging* 45(3): 471-95

¹⁵ Langbein, T, Weber, WA, Eiber, M. Future of Theranostics: An Outlook on Precision Oncology in Nuclear Medicine. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*, 60(Suppl 2), 2019,13S-19S

¹⁶ Zhang Jinrong, Luo Zhifu. The progress of radioisotope technology and application in China. *Strategic Study of CAE*, 2008;10(1):61-69

¹⁷ <https://baijiahao.baidu.com/s?id=1756725596698794889&wfr=spider&for=pc>

¹⁸ Peng Shuming, Yang Yuchuan, Yang Xia, et al. Development Strategy for Innovation System of Radiopharmaceuticals in China. *Strategic Study of CAE*, 2022,24(6):116-126

million nuclear medicine procedures in the United States and approximately 10 million procedures in Europe,¹⁹ while in China, the number of procedures is less than 3.5 million.

As of March 2022, the FDA had approved 60 radiopharmaceuticals (including 18 radioisotopes, containing Lutetium-177-DOTATATE and Lutetium-177-PSMA-617 which have breakthrough therapeutic effects on malignancies that pose serious threat to human health). As of the same timeframe, China's NMPA had approved only 30 radiopharmaceuticals, with no innovative radiopharmaceutical drugs approved in the past 10 years. Most radiopharmaceuticals currently used in clinical practice in China are generic drugs, and the drugs undergoing clinical research are mainly used for diagnostic purposes.

In 2021, eight ministries and commissions of the State Council jointly issued the *Medium and Long-term Development Plan for Medical Isotopes (2021-2035)*.²⁰ This was the first programmatic document issued in China supporting the application of healthcare related nuclear technology, leading to comprehensive and important deployments in the development and production of medical isotopes, research and development of radiopharmaceuticals, medical insurance policies, and overall industry layout. It is expected that the medical isotopes-based radiopharmaceutical industry will experience rapid growth in the coming years. In certain areas of China, including Chengdu (Sichuan Province) and Haiyan (Zhejiang Province), efforts are underway to accelerate the development of the nuclear medical health industry. By combining their own inherent strengths and advantages in the nuclear industry with China National Nuclear Corporation, other enterprises are also accelerating the pace of development within China's nuclear medical industry.

China faces several practical challenges regarding the development, production, and clinical application of radiopharmaceuticals, as well as with regard to radioactive waste management. When considering the overall safety of radiopharmaceuticals and the significant potential to elevate cancer treatment in China, further holistic optimization and improvement of the national policies and regulations will play an important role in accelerating the evolution of China's radiopharmaceuticals industry.

¹⁹ World Nuclear Association. Radioisotopes in Medicine, <https://www.world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine.aspx>

²⁰ China Atomic Energy Authority. Notice on Printing and Issuing the Medium and Long-Term Development Plan for Medical Isotopes. <http://www.caea.gov.cn/n6758881/n6758890/c6812195/content.html>

1. Optimize supervision frameworks and policies accommodating the characteristics of radiopharmaceuticals

1.1 Situational analysis in China

1.1.1 Strengthen leadership and coordination of cross-sectoral management

Unlike more conventional or regular medicinal products, radiopharmaceuticals also need to comply with stringent radiation protection and heightened environmental protection related regulations. In China, radiopharmaceuticals are subject to a highly regulated regulatory system. China's radiopharmaceutical regulatory framework includes all areas, including drug research and development, production, operation, and application. All procedures must be approved by the National (or provincial) Medical Products Administration, the Administration of Science, Technology, and Industry for National Defense, the Ecology and Environment Department, the Health Commission, the Transportation Department, the Public Security Department, and many other departments before receiving corresponding certificates and approvals.

In recent years, the state authority has successively introduced relevant measures to stimulate the development of market entities. These measures include transfer approval rights from the national regulatory agency to its provincial counterpart for radiation safety permits to produce radioisotope units in Class B and C sites, and radiopharmaceuticals production and operation enterprises.²¹ More reasonable planning has been made for the configuration of some large-scale medical equipment,²² while increasing the number of configurations and simplifying the overall relative management process. This said, multiple departments continue to be involved in the overall supervision of the radiopharmaceuticals industry. Cross-management by multiple departments leads to an overall lack of leadership and coordination, and with poor cohesion across the various agencies. By contrast, the oversight system in Europe and the United States is systematic and managed centrally according to the particularity of radiopharmaceuticals. This is managed by the relevant nuclear safety supervision committee²³ and drug supervision and administration agency.

²¹ State Council. Notice Regarding Deepening the Reform of Separating Permits from Business Licenses and Further Increasing the Development Vitality of Market Participants. http://www.gov.cn/zhengce/content/2021-06/03/content_5615031.htm

²² National Health Commission. Notice on the release of the 2018-2020 large-scale medical equipment configuration plan.

<http://www.nhc.gov.cn/zwgk/zxxxgk/201810/e5d3d478905a447cb9609b569680577d.shtml>

²³ The U.S. Nuclear Regulatory Commission. <https://www.nrc.gov/about-nrc.html>

1.1.2 The current laws and regulations should be strengthened to balance the special property of radiopharmaceuticals with both drugs and radioactivity

In the past few decades, the state has issued relevant management policies to strengthen the supervision and guidance of radiopharmaceuticals. These laws and regulations are strict and complex. Although some enhancements have been made, improvements to the holistic policy environment are needed for the industry to materially advance the clinical research and industrialization development of new radiopharmaceuticals in China. For example:

- When the drug regulatory authority regulates radiopharmaceuticals, it does not fully consider the special properties of "radioactivity" (e.g., natural decay (reduction), short half-life, some need to be synthesized in-hospital, low chemical quantity, etc.), but attempts to manage this in accordance with the provisions of conventional drugs.
- Agencies overseeing key areas, such as environmental protection, public security, and transportation have over-considered the radiation safety of radiopharmaceuticals especially in the circulation and use, regulating radiopharmaceuticals as radioactive substances while ignoring their unique attributes of being both safety and effectiveness as drugs, their limited half-life, high circulation frequency and high requirements for logistics. Collectively, this creates an underperforming ecosystem that undermines the industry's development in China.

1.2 Novartis recommendations

Regulation challenges hinder the speed and efficiency of research and innovation of radiopharmaceuticals, thereby limiting patients' timely access to treatment.

1.2.1 Improve cross-departmental supervision coordination system for radiopharmaceuticals

Given the large number of government agencies involved in the supervision of the radiopharmaceutical industry, it is essential that the regulatory coordination mechanism be improved. Sichuan Province has developed a potential coordination reference model. Sichuan Province attaches great importance to the coordinated development of the nuclear technology application industry, especially the radiopharmaceutical industry, and has established an interdepartmental coordination mechanism. The Bureau of Economic Cooperation, the Economic and Information Department, the Department of Ecology and Environment, the Health Commission, the Healthcare Security Administration, and the Medical Products Administration have established a special interdepartmental service mechanism to promote the radiopharmaceutical industry development, and jointly issued the

*Action Plan for the Development of Medical Isotopes and Radiopharmaceuticals Industry in Sichuan Province (2022-2025).*²⁴

It is highly recommended that China create an interdepartmental coordination mechanism at the national and provincial levels to help improve the holistic management of the radiopharmaceuticals industry. In so doing, multiple departments would be tasked with strengthening communication and jointly addressing regulatory challenges. In February 2023, the General Office of the State Council issued the *Guiding Opinions on Deepening Comprehensive Supervision across Departments*.²⁵ This proposed that matters involving multi-sectoral supervision of key sectors, such as pharmaceuticals and emerging areas, should be actively carried out and accelerated. The radiopharmaceuticals industry would greatly benefit from such an approach.

1.2.2 Conduct scientific supervision while balancing its unique property of being both a medicine and having radioactive properties

Revise and improve existing policies to make them more applicable and feasible. For radiopharmaceuticals, drug regulatory authorities should adopt different review concepts and strategies. Relevant technical evaluation systems can be established to meet the unique characteristics of radiopharmaceuticals such as improving the definition of radiopharmaceuticals and establishing technical guidelines for pharmaceutical research and quality standards.

Medical isotopes radiation toxicity is known, and the dosage is lower than that of other radioactive industries and can be distinguished from other radioactive substances to balance their distinctive pharmaceutical characteristics. At the same time, relevant radiation protection and environmental protection policies should be adjusted to reflect newer therapeutic nuclides appropriately and scientifically. Unlike other radioactive materials, many new radiopharmaceuticals are injected directly into the human body for treatment, thereby greatly minimizing any transport risk. This is a significant contrast from other radioactive substances. As a result, it is possible to substantially simplify the requirements for vehicles and key personnel involved in radiopharmaceuticals transport.

²⁴ Sichuan Provincial Committee of Civil Military Integration Development Office, etc. *Action Plan for the Development of Medical Isotopes and Radiopharmaceuticals Industry in Sichuan Province (2022-2025)*. https://mp.weixin.qq.com/s?__biz=Mzg2MDg2ODMyOQ==&mid=2247483877&idx=1&sn=d6095c3b1771382161c7a3c318f7ad15&chksm=ce1e9a63f9691375a590da592dad4cd7626c9b03621b7e3f983c63dc0c6ffd06c865787b45d0&mpshare=1&scene=1&srcid=0215LUUbN1w7VLJuDM2Owhxh&sharer_sharetime=1676419418135&sharer_shareid=f101167f4541c3fccb6bba87500c747#rd

²⁵ General Office of the State Council. *Guiding Opinions of the General Office of the State Council on Deepening Cross-departmental Comprehensive Supervision*, http://www.gov.cn/zhengce/content/2023-02/17/content_5741898.htm

2. Support the construction and development of nuclear medicine departments to better meet the needs of clinical applications

2.1 Situational analysis in China

Radiopharmaceutical diagnosis and treatment must be conducted in medical institutions, while use of certain radioisotopes also requires hospitalization. Regulations strictly manage the medical institution's nuclear medicine department. The relevant workplace must be shielded and protected; the treatment ward area and the isolation area must meet strict radiation safety protection standards for a particular radiotherapy treatment; and patient discharge standards must strictly adhere to the corresponding regulations.²⁶

As more new radiopharmaceuticals become available for clinical use, the number of eligible patients grows, as do the clinical needs. This said, the number of existing authorized medical institutions are insufficient to provide adequate healthcare service.

2.1.1 It is difficult for medical institutions to obtain the licenses and qualifications necessary to conduct new radiopharmaceutical treatment

In order for medical institutions to use radiopharmaceuticals for diagnosis and treatment, they must first obtain multiple licenses and qualifications (e.g., *Radiation Safety License*, *Radiotherapy License* and *Radiopharmaceutical Use License*) and relevant staff must acquire professional qualifications and practice licenses and complete the necessary nuclear medicine training. Each licensing application for the use of radiopharmaceuticals has strict restrictions and intricate procedures. The hospital is also subject to the relevant nuclide quota restrictions and cannot exceed the maximum daily equivalent operating volume and the maximum equivalent annual dosage, which are specified in the *Radiation Safety License*. Additional approval is required for adding a new isotope or increasing the quota of an existing isotope, and in some cases the modification of the department's current hardware facilities is needed.

2.1.2 For novel radiopharmaceuticals treatment, the Nuclear Medicine Department needs to improve the readiness of professionals and infrastructure

The implementation of new radiopharmaceuticals treatments, e.g., radioligand therapy, is an immense challenge that involves the integration of diagnosis and

²⁶ National Health Commission. Nuclear Medicine Radiological Protection Requirements. <http://www.nhc.gov.cn/cms-search/downloadFiles/657e04bc556e428db6db6f4bc98191a7.pdf>

treatment, including training for medical professionals, as well as the need for sophisticated equipment and technically designed facilities.

The treatment carried out in nuclear medicine departments in China currently remains uneven. According to the 2019 census data, only 770 nuclear medicine departments are allowed to perform radionuclide treatment, with 2,544 beds and approximately 12,500 nuclear medicine-related staff (of which only 20% have senior professional titles). Iodine-131 treatment is the majority, and the proportion of new radionuclide treatment is less than 1%.²⁷ In many cases, the comprehensive supporting facilities of the nuclear medicine department in some hospitals are yet to be upgraded. The infrastructure should be updated to meet the new requirements of radiation protection safety supervision. As an example, the requirements for radioactive waste treatment are becoming increasingly strict. The 2021 *Radiation Protection and Safety Requirements for Nuclear Medicine (HJ 1188-2021)*²⁸ imposes stricter requirements for the temporary storage time of radioactive waste, while the total volume of the decay pool in the hospital is limited. As a result, hospitals cannot undertake the treatment task of more patients.

2.1.3 The relevant specifications and standards for clinical application of radiopharmaceuticals are unclear

The department of nuclear medicine lacks a standardized regulation for the application of radiopharmaceuticals, and this may not be conducive to the development of clinical practice. Furthermore, there are no applicable clinical application requirements and standards for innovative therapeutic nuclides. This concern is demonstrated by the use of Lutetium-177 in clinical settings in China. This promising new therapeutic radionuclide, Lutetium-177, has undergone extensive clinical studies and application both abroad and in China. Despite its widespread application, China has not yet implemented radiation protection requirements for Lutetium-177 patients, there is also no unified standard regarding the length of stay after receiving Lutetium-177 treatment or the requirement for radioactivity when discharged, and its radiation safety management needs to be further clarified.

2.2 Novartis recommendations

Increasing hospital capacity and upgrading infrastructure are necessary steps to improving care and overcoming diseases. Measures can be taken in the following areas:

²⁷ Chinese Society of Nuclear Medicine. A Brief report on the results of the national survey of nuclear medicine in 2020. *Chin J Nucl Med Mol Imaging*, 2020,40(12),747-749

²⁸ Ministry of Ecology and Environment. The Radiation Protection and Safety Requirements for Nuclear Medicine. https://www.mee.gov.cn/ywggz/fgbz/bz/bzwb/hxxhj/xgbz/202109/t20210922_952244.shtml

2.2.1 Optimize the licensing application procedure for clinical use of radiopharmaceuticals, increase the quotas of medical isotope at medical institutions

Gaining the support of relevant regulatory authorities, participating in the review of relevant licensing applications in advance, enhancing communication and guidance, as well as optimizing the licensing application procedures for radiopharmaceuticals used in hospital are a few of the recommended measures that should be taken.

Under the safety supervision and management of medical isotopes, the approval of radiation safety permits for the use of medical isotopes in hospitals needs to be accelerated, with an appropriate increase in the medical isotope quotas for medical institutions. Additional flexibility in the total limit of isotopes used in radiopharmaceuticals should also be considered.

2.2.2 Offer necessary assistance and guidance for healthcare personnel and hospitals (including hardware facilities and training, etc.)

The quality and safety of patient care must be guaranteed. The state proposed to strengthen infrastructure construction during the *14th Five-Year Plan* period, thereby popularizing the construction of nuclear medicine departments in tertiary hospitals. Further formulation and promulgation of specific implementation plans is needed. It is important to consider the substantial benefits that the newly developed radioligand therapies will bring to patients upon approval. Hospitals in major cities can be designated to build first-class nuclear medicine departments with advanced conditions, infrastructure, and software, including waste liquid treatment systems. In those hospitals, training of nuclear medicine personnel should be reinforced to increase the number and professional level of nuclear medicine practitioners. To ensure the quality and safety of patient diagnosis and treatment, it is essential that these medical professionals have the ability and capacity to conduct procedures with new radiopharmaceuticals.

2.2.3 Establish relevant standards for clinical use of radiopharmaceuticals and enhance radiation safety management

Introduction of relevant regulations for the appropriate clinical use of radiopharmaceuticals can aid in the unification of the essential requirements for their use. Radiation safety management standards and regulations for new therapeutic nuclides should be established. Lutetium-177, as a therapeutic nuclide recommended by The International Atomic Energy Agency, has been widely used in many countries, and its radiation safety protection regulations are flexible among

countries and regions. According to Australian clinical practice experience,²⁹ patients in Australia receive treatment in the outpatient department of hospital and stay for about 4 hours prior to being discharged. It is encouraged to develop relevant standards, such as radiation protection requirements and waste disposal requirements, collect clinical monitoring data, take international experience as reference and benchmark, improve HJ 1188-2021 standards on waste disposal, and provide reference for relevant management suggestions.

3. Further improve patient access to medicines

3.1 Situational analysis in China

Radiopharmaceuticals require a systematic approach from diagnosis to treatment. Accurate diagnosis could be used for disease staging, disease identification, patient screening and treatment outcomes evaluation. For nuclear medicine department diagnosis and treatment services, the *National Medical Service Item* established a category designated "nuclear medicine" which falls under "medical technology diagnosis and treatment". Every province also issues its own catalogue of medical services items and self-regulates the price of various service items. The National Reimbursement Drug List (NRDL) 2022 includes 9 radiopharmaceuticals, all classified as diagnostic radiopharmaceuticals. The NRDL currently does not have a category for therapeutic radiopharmaceuticals.

3.1.1 Limited national or regional comprehensive pricing model and basis

In order to accelerate the creation of a scientific healthcare service pricing mechanisms with dynamic adjustment and optimize the healthcare service pricing structure, the National Healthcare Security Administration (NHSA), the National Health Commission and other departments jointly issued the *2021 Pilot Plan for Deepening Medical Service Price Reform* to explore the formulation of price item preparation specifications, to improve national price item specifications and to optimize management of newly added pricing items.³⁰ Based on this, NHSA has updated the *National Medical Service Program*, and each province also updated the local *Catalogue of Medical Service Price* accordingly. On the charging of diagnosis and treatment of radiopharmaceuticals, medical service project codes have been established for some nuclear medicine-related services in the *National Medical Service Program*, clarifying the connotation, exclusionary content, and pricing unit

²⁹ Louise Emmett, Kathy Willowson, John Violet, et al. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci*, 2017 (64) :52-60

³⁰ National Healthcare Security Administration. Pilot Plan for Deepening the Medical Service Prices Reform. http://www.nhsa.gov.cn/art/2021/8/31/art_14_5894.html

of the item,³¹ while local healthcare security administrations formulate specific local fee standards.

Despite the *National Medical Service Program* implemented at the national level, there remains a vast difference across the provinces regarding the item connotation, exclusionary content and pricing basis in the charging and management of clinical application for radiopharmaceuticals. This leads to an inconsistent value recognition standard for technical services of medical service items for radiopharmaceuticals across the country, including a lack of effective connection with nuclear medicine department construction standards and management principles for medical staff. This is not conducive to the promotion of standardization construction of nuclear medicine departments. The variation of radiopharmaceutical prices between regions is related to the economic development level, medical technology advancement level and affordability of all parties, which has created barriers for patients to receive cross-regional radiopharmaceutical diagnosis and treatment.

3.1.2 Medical insurance classification for therapeutic radiopharmaceuticals has yet to be established

To reduce the burden on patients, diagnostic radiopharmaceuticals were introduced in the 2017 NRDL for the first time in February 2017.³² Since then, the state has also actively explored the promotion of including more eligible radiopharmaceuticals within the scope of reimbursement. However, there are currently no designated medical insurance policies specifically indicated for radiopharmaceuticals and which are included in the medical insurance system together with non-radioactive drugs. Although diagnostic radiopharmaceuticals are included in the NRDL, there is currently no clear classification for therapeutic radiopharmaceuticals. This leads to poor functional positioning of radiopharmaceuticals by medical insurance agencies, and to differences between the use mode of radiopharmaceuticals and the medical insurance classification. This results in confusion between clinical management and medical insurance management. At the same time, the medical insurance access path of therapeutic radiopharmaceuticals is unclear, indirectly hindering the exploration of therapeutic radiopharmaceuticals to reduce the burden of patients and improve the willingness

³¹ National Healthcare Security Administration. National Medical Services Program. [https://code.nhsa.gov.cn/ylfw/stdMedicalService/toPublicStdMedicalServiceStandardList.html?batchNumber =](https://code.nhsa.gov.cn/ylfw/stdMedicalService/toPublicStdMedicalServiceStandardList.html?batchNumber=)

³² Ministry of Human Resources and Social Security. Notice Regarding the Printing and Issuing of the National Drug Catalogue for Basic Medical Insurance, Work Injury Insurance and Maternity Insurance (2017). http://www.mohrss.gov.cn/SYrlzyhshbzb/shehuibaozhang/zcwj/yiliao/201702/t20170223_266775.html

of patients to pay through medical insurance, and thus slows down the pace of improving the accessibility of therapeutic radiopharmaceuticals.

3.2 Novartis recommendations

3.2.1 Establish a national or regional comprehensive pricing model and charging basis in line with actual diagnosis, treatment technology and labor costs

Use integrated diagnosis and treatment and multidisciplinary joint decision-making models to promote the clinical application of nuclide molecular diagnosis and nucleotide ligand therapy which belong to innovative targeted precision therapies. From diagnosis to treatment, it needs to be completed under a strict process, high-quality supervision and comprehensive cooperation of doctors, technicians, and nurses, requiring extremely good hardware facilities and high-quality operating costs. A comprehensive national and regional pricing model is recommended that considers actual diagnosis, treatment technology and labor costs. This would more appropriately reflect the technical service cost of the relevant medical and technical personnel, and gradually eliminate regional differences.

3.2.2 Promote more innovative radiopharmaceuticals to be included in NRDL and establish a classification for therapeutic radiopharmaceuticals

Substantively promote more innovative radiopharmaceuticals to be included in the NRDL, explore establishing the classification of therapeutic radiopharmaceuticals based on the existing classification with diagnostic radiopharmaceuticals in the NRDL. Action should be taken to further improve the evaluation criteria of relevant radiopharmaceuticals, fully consider its technical innovation and comprehensive management requirements, and formulate reasonable payment standards or innovative payment schemes to improve patients' accessibility and the affordability of radiopharmaceuticals.

Conclusion

Biomedicine is making major breakthroughs at unprecedented speeds and having access to new and revolutionary treatment solutions can help patients to live healthier and longer lives. With the increasingly prominent role of radiopharmaceuticals in the diagnosis and treatment of major diseases, the multi-level and diversified demand will continue to grow. Novartis, as an innovative pharmaceutical company, is a pioneer and leader in the development of precise targeted drugs containing radioactive ingredients. Based on the experience accumulated in such highly specialized technical solutions, we are willing to work with and to support the Chinese government in its efforts to provide people with comprehensive and full-cycle health service, especially in the development of

innovative radiopharmaceuticals, and make this advanced solution institutionalized, ultimately benefiting patients.