Improving the Evaluation Framework of NRDL Dynamic Update for Innovative Drugs in China

Jointly Proposed by Chinese Academy of Labor and Social Security, Beijing Pharmaceutical Healtheconomics Research Association, IQVIA Real-World Insights

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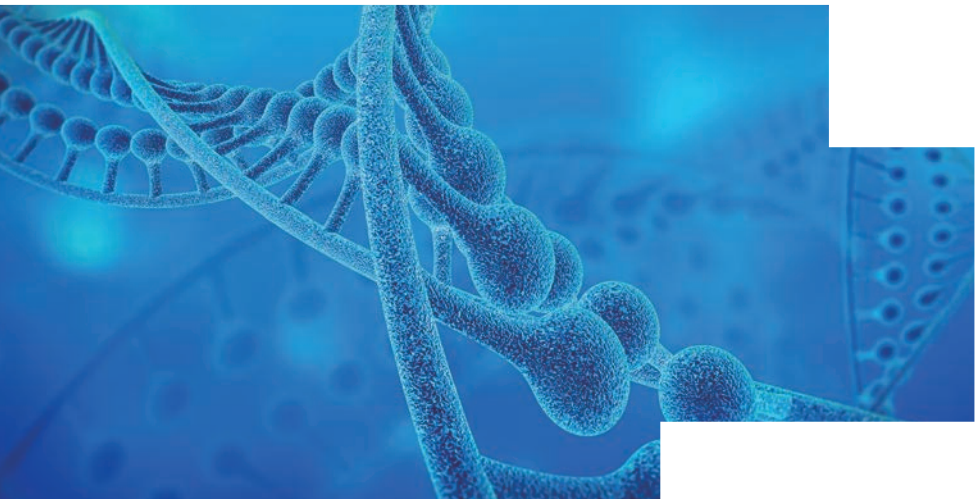

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Background

Accelerating the NRDL updates has become the key to further improvement of the accessibility of new drugs

Over the past 40 years, china's economy has been developing rapidly, consolidated national strength and growing international influence have been significantly enhanced, and people's living standards have markedly improved, laying a solid foundation for cultivating further innovation and improvements in quality of life. At the 18th Communist Party of China (CPC) National Congress, the CPC Central Committee, with President Xi Jinping at its core, declared national health as an important basis for the overall well-being of Chinese society, emphasizing a call to action to prioritize population health during this development era. As a result, in October 2016, the CPC Central Committee of China and the State Council issued the Outline Plan for "Healthy China 2030" to accelerate the establishment of "Healthy China" alongside overall economic and social development. The policy document included important goals such as strengthening public health services covering the nationwide population, improving the health insurance system, providing high-quality and efficient healthcare services, strengthening health services for key populations, propelling health science and technology innovation, promoting the development of the pharmaceutical industry, and emphasizing important goals such as institutional reform.

After 20 years of efforts, China has now established a universal social health insurance that greatly enhanced the accessibility of basic medical services for the general population. With rising social standards and improved health insurance, patient demand for new drugs has also gradually become level with international standards. Since 2015, the pace of new drugs entering the Chinese market has quickened due to faster review and approval of new drugs by drug regulatory authorities; over time, the generic quality consistency evaluation will also lead to improvement of the overall quality of generic drugs. In this context, the public has put forward higher expectations for increasing the frequency of drug listing updates.

In accordance with the Interim Measures on the Administration of the Scope of the Drug Use of Basic Health Insurance for Urban Employees issued by the Ministry of Labor and Social Security in 1999, the National Reimbursement Drug List (NRDL) for Basic Health Insurance should be updated once every

two years, and the addition of new drugs into the NRDL should be performed once per year. However, in practice, doing so proved to be much more sophisticated than expected, and consequently the frequency of drug listing updates has failed considerably to match its pre-established standards. In fact, the NRDL for Basic Health Insurance has only been revised three times (in 2004, 2009 and 2017) since its inception in 2000, with the gaps between revisions being 4 years, 5 years and 8 years, respectively. It is evident that the current update frequency of the NRDL fails to keep up with the growing needs of the population and the ceaseless development of medical science and technology. After 2017, this situation has improved.

In April 2017, the Ministry of Human Resources and Social Security issued the Notice on Public Solicitation for Suggestions on Establishing and Improving the Dynamic Update Mechanism of the NRDL for Basic Health Insurance, inviting research institutions, academic groups and people from all walks of life to propose suggestions for the NRDL´s dynamic update mechanism. The Notice has listed key questions to be considered for NRDL dynamic updates, including: (1) how to balance clinical needs, support for innovation, and the affordability of health insurance funds; (2) what measures and rules should be adopted for evaluation of newly-approved drugs, patented drugs, and non-exclusive varieties for inclusion into health insurance coverage; (3) how to make full use of pharmacoeconomics and other evaluation methods to support the expert review mechanism; (4) how to link up with payment standards; and (5) how to effectively connect drug registration review with approval, production, circulation, clinical use and medical reimbursement.

It is noteworthy that, in 2017, 2018, and 2019, the national health insurance authority held three negotiations on innovative drugs that enabled the prices of approved drugs to decrease by more than 50%, significantly relieving the economic burden of patients and it´s welcomed by all sectors of society. Since the establishment of the National Healthcare Security Administration in 2018, the health insurance authority has also undertaken the functions of drug procurement and price management, implying that the authority might be able to sign more diversified negotiation contracts with greater flexibility in determining reimbursement payment standards and various procurement conditions for NRDL inclusion.

These three negotiations on medical insurance of innovative drugs are large-scale exploration of the

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access mechanism of innovative drugs at the national level. The modalities and paths adopted in these negotiations have laid a practical foundation for the future development of China´s access mechanism; these recent developments also imply that the NRDL entry pathway for innovative drugs has begun to accelerate. Nevertheless, from the current negotiation process and execution, there are rooms to be improved in the current negotiation process, as some detailed rules need to be standardized and supporting policies need to be further specified.

In this study, we conducted in-depth interviews with R&D manufacturers, health economic specialist, medical and pharmaceutical specialist on the first three innovative drug negotiation. The conversations centered around the connection between the negotiation of innovative drugs and the selection of NRDL, the issues that need to be further standardized in the negotiation, the technical support needed in the negotiation, the diversified forms of the negotiation contract, and the specific strategies to implement the negotiation results under the background that put the innovative drug negotiations into the NRDL dynamic adjustment. Literature on the access and price formation of innovative medical insurance in countries/regions such as the United Kingdom, Germany, Canada, Australia, France, Japan and Taiwan China have also been collated as potential models for China´s developing pharmaceutical access infrastructure.

Summary

Main suggestions for building dynamic NRDL adjustment mechanism

I.It is suggested to clarify the frequency of yearly adjustment of innovative drugs in the National Reimbursement Drug List (NRDL), set the negotiation on innovative drugs as a regular module, make clear the links and channels for companies to participate in, and further ensure the fairness of decision-making procedures by improving the expert withdrawal system.

II.The access process of innovative drugs through national negotiation is: (1) the drugs applied for inclusion to the NRDL will be classified into innovative drugs and non-innovative drugs by the innovation evaluation; (2) economic innovative drugs will be classified into the scope of regular access, while drugs identified as lack of economic value will be classified into the scope of negotiation by the economic evaluation; (3) a voting process will be carried out by a group of 10-30 clinical, medical insurance, pharmaceutical economics experts and insured representatives by international standards, who will vote to decide the inclusion of NRDL for economic innovative drugs and non-innovative drugs, and the eligibility of non-economic innovative drugs to enter negotiation.

III.It is suggested to further optimize the organizational structure, establish a third-party review authority as soon as possible, and clarify the responsibilities of the administrations, the review authority, the review expert group, the voting organization and the negotiation group.

IV.During the innovation evaluation, the main dimensions such as innovation value, clinical value, patient value and social value should be considered comprehensively, and quantitative and standardized assessment tools should be used. For products with different innovation levels, it is suggested to use differentiated assessment methods and criteria to determine the medical insurance reimbursement standards based on the international experience.

V.During the economic evaluation, the standardized and quantitative tools should be used to calculate the cost-effectiveness of new drugs scientifically and accurately, considering the changes in clinical benefits and costs comprehensively. It is necessary to have a good knowledge of the complex factors influencing the actual price in different countries when using the international reference price as a pricing tool to reasonably determine the specific method applicable for China to calculate the external reference price.

Summary

VI.In order to facilitate the parties to reach an agreement on the evidence relevant to drugs, it is suggested to further improve the pre-formal negotiation communication mechanism after the formation of review comments to provide formal feedback to companies on the supplements required to be submitted.

VII.In order to avoid the situation that the price is too low due to the difference between groups and to protect the companies´ motivation from the long-term perspective, it is suggested to add the mechanism of minimum price protection to the current price negotiation rules.

VIII.It is suggested to adopt more diversified contract signing forms, such as volume- and price-based contract, purchase-and-give contract and efficacy-based risk contract commonly used internationally, which may help to reach an agreed price. The contract executed in the initial negotiation may formulate the renewal conditions, as well as the price change mechanism and delisting mechanism for the renewal.

IX.It is suggested that the results of the negotiation should be made public in an appropriate form, with reference to the international practice, so as to improve the fairness and transparency of government decision-making.

X.The successful implementation of the innovative drug negotiation system depends on the consensus among multiple departments. Therefore, data sharing and primary data construction of the medical system should be strengthened, and supporting policies to ensure the implementation should be formulated.

The framework for dynamic NRDL updates

The 2017 and 2019 NRDL update demonstrated that innovative drug negotiations are constituent parts to the NRDL update process. NRDL listing decisions for the majority of drugs are directly made by a selected panel of experts; at the same time, a list of high-price innovative drugs is proposed for further detailed evaluation and negotiation. Practice has proven that this approach is effective. But some details need to be clarified and perfected.

I. Key imperative issues for establishing NRDL dynamic adjustment mechanism

The four recent NRDL updates since 2004 and the three negotiations on innovative drugs have established a basic framework for the update mechanism. To increase the efficiency of review and selection, promote normalization of processes and increase the frequency of NRDL updates, the following issues should be clarified on the basis of the prior framework:

Clarify the frequency of NRDL updates and reflect "dynamic":

NRDL drug listings require strict process of evaluation and expert selection; for innovative drugs, negotiations are also necessary. Overall, it is estimated that 8-9 months are needed to complete a listing update, 3-4 months are needed for innovation drug´s negotiation. But it only took 5 months for the 2008 special negotiations on anticancer drugs go from selection to negotiation. Based on the current situation, it is feasible to update the innovation drugs every year; enterprises can be considered to submit applications independently in real time to reflect the "dynamic" characteristics.

Define innovative drug negotiation as a component of dynamic NRDL updates and access by category

Innovative drugs and non-innovative drugs adopt access by category. Most drugs are non-innovative and may be substituted by competitive alternatives in the market, the existing drug listing procedures can be applied for these drugs. Meanwhile, a few innovative drugs are expensive, clinically needed and unlikely to be substituted by existing drugs. In such cases, the medical insurance side needs to negotiate with the pharmaceutical companies to get it into the list. These drugs should only be listed if acceptable prices are negotiated between health insurance payers and pharmaceutical manufacturers.

Identify channels for manufacturer participation in the dynamic NRDL update process

In the short term, the NRDL can be adjusted once a year, and enterprises shall submit relevant

The framework for dynamic NRDL updates

materials according to regulations. In the international experience reference, the most pharma-developed countries referenced, manufacturers are allowed to directly submit product applications for reimbursement listing. Therefore, as China´s health insurance management strengthens and matures, manufacturer-initiated applications could also be considered for the NRDL update process, which is helps to relieve the time pressure of concentrated expert review. Application materials are to include basic product characteristics and descriptions of product innovativeness and economy to support evidence-based decision-making. In addition, allowing the communication about the relevant evidences of drug between manufacturers participating in negotiation and the health insurance authority will encourage for the two parties to reach a consensus on relevant evidence when needed.

Emphasize the objectivity, fairness, and transparency of the evaluation process

NRDL evaluation is a public decision-making process, so a system of standardized procedures must be established for dossier submissions, expert avoidance, informational disclosure, and so on, to ensure scientific robustness, fairness and transparency.

Reference to International Practice

The update frequency is rather high in countries and regions with established drug listing mechanisms (Fig.1). For example, the Australian Pharmaceutical Benefits Advisory Committee (PBAC) holds three meetings each year to vote on drugs newly included into the reimbursement list [1]; the Canadian Drug Expert Committee (CDEC) holds 12 regular meetings each year[2]; and the Pharmaceutical Benefit and Reimbursement Scheme Joint Committee meet at least 6 times each year in Taiwan[3].

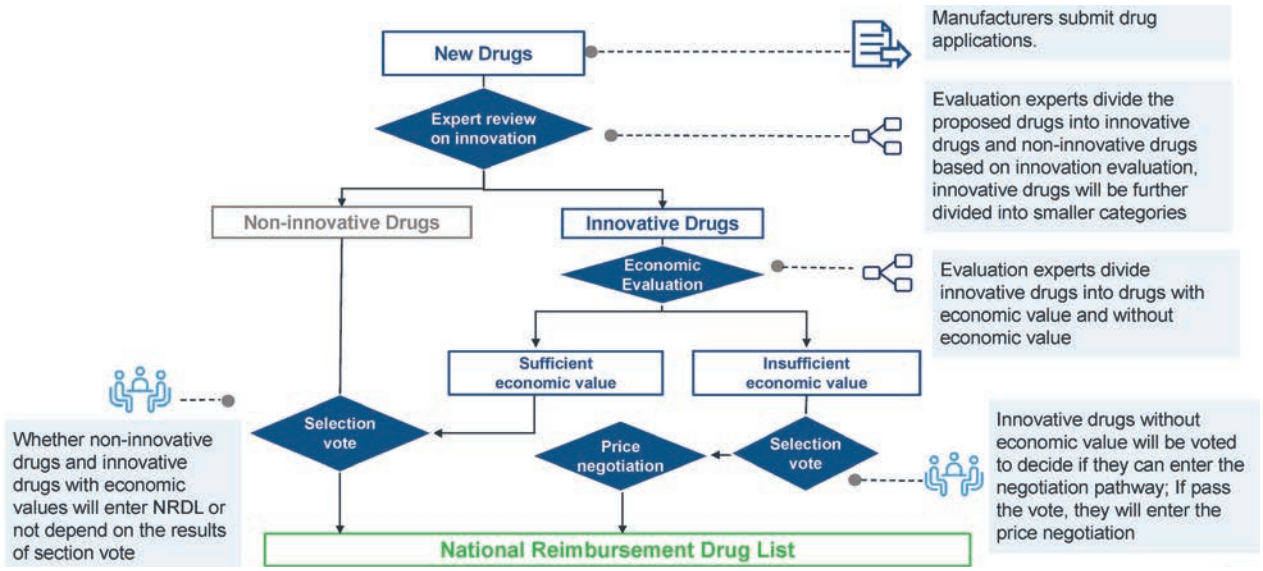
Fig.1 Meeting Frequency of Selected Committees

Sources: desk research, IQVIA analysis

II. Basic concept of classified NRDL listing

In dynamic NRDL adjustment, innovative and non-innovative drugs could develop in the same process. However, considering the differed characteristics of economic evaluation and price formulation rationale, the concept of classified evaluation and inclusion should be adopted (Fig.2).

Fig.2 Illustration of the Classified Inclusion Framework.



Sources: IQVIA analysis

The concept of classified inclusion is outlined as follows: (1) evaluation experts divide the proposed drugs into "innovative drugs" and "non-innovative drugs" based on innovativeness assessment, of which innovative drugs may be further classified; (2) For innovative drugs, evaluation experts will divide them to economical and non-economical according to the economical evaluation results; (3) According to the voting group´s results to determine whether the non-innovative drugs and economical innovation drugs should be include in the list and whether the non-economical innovation drugs should be include in the negotiation scope. If yes, the price negotiation should be conducted.

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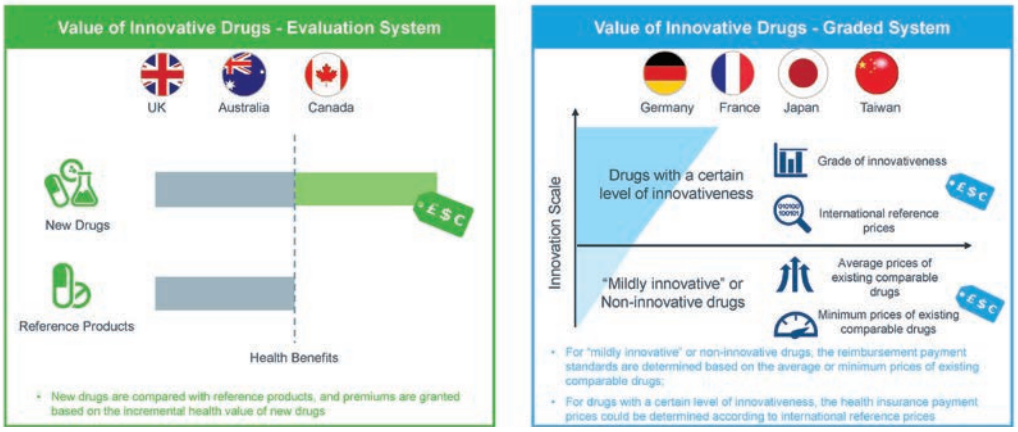
The rationale behind classified inclusion is based on the price reference difference between innovative drugs and non-innovative drugs. For non-innovative drugs, products of the same kind that are competent as substitutes are already included in the NRDL. Although these drugs may be "new drugs" in terms of composition, their efficacy is not markedly innovative. This practice can promote price competition among drugs of the same kind. While for innovative drugs, no drugs with similar efficacy are included in the NRDL. Therefore, it is impossible to determine the medical insurance payment price according to the existing price of similar drugs. Moreover, such innovative drugs are often in a non-competitive market and may be relatively expensive, which means including them directly into the NRDL may have major impacts on the health insurance fund. Therefore, the practices of other countries and regions such as the United Kingdom and Germany with experience are referenced: establish a relatively mature health technology assessment system, and check and ratify the premium for innovation drugs according to the innovation value grading or pharmacoeconomics quantitative evaluation. (Fig.3).

Reference to International Practice

The United Kingdom. Australia, Canada, Germany, France, Japan and Taiwan, China all established evaluation of drug innovation value.

Fig.3

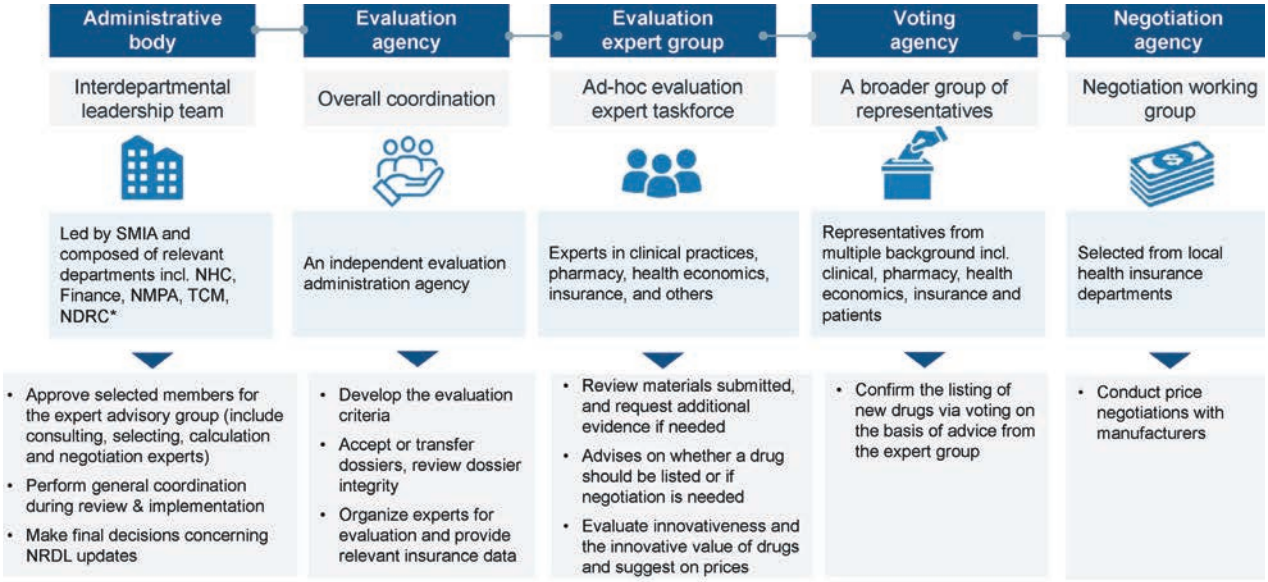


Sources: desk research, IQVIA analysis

III. Organization structure and responsibilities in NRDL adjustment

The organizational structure for the current NRDL update process may be generally adapted for current dynamic NRDL updates, though the roles and responsibilities of each party should be further specified (Fig.4).

Fig.4 Illustration of Organizations and Their Functions in Dynamic NRDL Updates



Note: NHC: National Health Commission; SMIA: State Medical Insurance Administration; NMPA: National Medical Products Association; TCM: Traditional Chinese Medicine; NDRC: National Development & Reform Commission
Sources: desk research, IQVIA analysis

Administrative Body (Interdepartmental Leadership Team)

The National Healthcare Security Administration is the administrative body in charge of the NRDL update process, including innovative drug negotiation. During previous updates, an interdepartmental leadership team was established and headed by the health insurance authority and composed of relevant departments for health, finance, drug administration, traditional Chinese Medicine, development

The framework for dynamic NRDL updates

and reform, etc. The leadership team is responsible for making final decisions concerning NRDL updates, performing general coordination during the review and implementation process, approving the selected members of the NRDL Expert Advisory Group, the Selection Panel and the Negotiation group, and communicating with relevant governmental departments and local health insurance departments. A dedicated office may be set within the administrative body to handle related affairs in the above-mentioned NRDL update process.

In other countries, the functions of the decision-making body are mainly assumed by the healthcare security administration, e.g. the Federal Joint Committee (Gemeinsame Bundesausschuss/G-BA) in Germany, the National Union of Health Insurance Funds (Union nationale des caisses d'assurance maladie/UNCAM) in France, and the Central Social Insurance Medical Council in Japan (Chuikyo).

Evaluation Agency (Coordinator Role)

In the current mechanism, no permanent evaluation agency exists, as corresponding functions are mainly assumed by an administrative office temporarily set up within the administrative body. To support the normalization of the NRDL update process, a dedicated evaluation agency should be established and its accountable to the executive branch. Its functions may include: developing the screening criteria for inclusion and exclusion of drugs, the format of dossier submissions, drug medical insurance negotiation regulations, drug pricing rules, and so on, all of which will come into effect after approval by the administrative body; accepting and transferring dossiers and reviewing dossier integrity; organizing experts for evaluation and providing relevant basic data on health insurance to expert groups; coordinating communication among applying enterprises, expert groups and the leading team; and providing evaluation conclusions to the administrative body.

Responsibilities of this agency would be similar to those of the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Pharmaceutical Benefits Advisory Committee (PBAC) in Austria, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/IQWiG) in Germany, the French National Authority for Health (Haute Autorité de santé/HAS) in France and the Health Insurance Review & Assessment Service (HIRA) in Korea.

Evaluation Expert Group

A temporary evaluation expert group could be convened by the evaluation agency according to the therapeutic field of the evaluated drug. The expert group may be composed of experts in clinical medicine, pharmacy, pharmacoeconomics, health insurance, etc. The members are to be recommended by relevant academic groups and industry associations, and are academic leaders in relevant fields with respectful reputations and strong professional abilities. Expert selection in some professional fields, e.g. pharmacoeconomic evaluation, may be entrusted to professional agencies with open and reasonable procedures.

The main functions of the expert evaluation group include: (1) evaluating dossiers submitted by applicants, assessing their authenticity and scientific robustness and proposing requirements for supplemental evidence; (2) proposing review comment about whether a drug is innovation and economy; (3) grouping drugs of the same kind and proposing suggestions based on reference prices of drugs of the same kind; and (4) proposing suggestions on prices for drug which need negotiation.

The evaluation expert group functions like the "expert advisory group" in the current NRDL evaluation and negotiation process; however, in a dynamic NRDL updating environment, more emphasis will be placed on review, with more standardized outcome evaluations. The expert avoidance system should be strictly implemented for all evaluation experts. Avoidance will be required if the individual is of the following circumstances:

- An employee of the applying manufacturer or its affiliated manufacturers.
- A developer of the drug under application.
- A main participant in the preparation of the manufacturer´s application dossiers.
- If any important data in the dossier submitted by the manufacturer are quoted from study results of an expert, the expert needs to claim whether the study has been sponsored by the manufacturer; if the study has been sponsored by the manufacturer, the expert also needs to be absent from the evaluation.

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– The immediate family members hold posts in relevant enterprises, have received corporate project funders in the past two years, or hold stocks of relevant enterprises, which also need to be avoided.

Voting Panel

The voting panel is equivalent to "selection panel" in the dynamic NRDL adjustment. The current "selection panel" consists of thousands of members from each province, which often results with overly lengthy voting periods that would significantly hinder dynamic updating. Additionally, members of the selection panel are mainly doctors from medical institutions, hence there is a lack of representatives with other backgrounds (e.g. economics, statistics, humanities) and representatives of insured individuals and insured unit. Thus, it is suggested that voting panel representatives be diversified to include academics in clinical medicine, pharmacy, economics, insurance and other fields, as well as representatives of insured persons. However, the group size does not need to be large; referencing other countries (regions), a group with dozens of members is sufficient. Experts on the voting panel may serve for a period of time while representatives of insured persons may be temporarily recommended.

Negotiation Working Group

According to international practices, generally the negotiation working group is a concurrent role of the office directly under the administrative body. In the oncology drug negotiation in 2018 and innovative drug negotiation in 2019, a negotiating working group led by representatives of local health insurance authorities was established. This working group can allow joint decision-making for negotiations by local and central governments and should therefore be preserved. The main function of this group is: according to the recommendations of the review expert group, conduct detailed price negotiation with the negotiation enterprises, and finally form the medical insurance payment standard.

Reference to International Practice

In countries and regions referenced in this study, four agencies are involved in updating reimbursement drug lists: a decision-making agency, a work coordination agency, an evaluation agency and a voting agency (figure 5).

Fig.5 Examples of institutional arrangements

Country /Region	Decision-making body	Appraisal body	Voting body	Negotiation body
Australia	Ministry of Health	Pharmaceutical Benefit Advisory Committee(PBAC)	PBAC	Ministry of Health
Germany	Federal Joint Committee (G-BA)	Institute for Quality and Efficiency in Healthcare(IQWiG)	G-BA plenum	National Association of Statutory Health Insurance Funds(GKV-SV)
France	National Union of Health Insurance Funds (UNCAM)	National Authority for Health(HAS)	Transparency Committee(TC), Economic & Public Health Evaluation Committee	Economic Committee for Health Products (CEPS)
Canada	Provincial health insurance departments	Canadian Agency for Drugs and Technologies in Health (CADTH)	Canadian Drug Expert Committee (CDEC)	pan-Canadian Pharmaceutical Alliance(pCPA)
Korea	Ministry of Health	Health Insurance and Review Assessment (HIRA)	Pharmaceutical Benefit Committee (PBC)	National Health Insurance Service (NHIS)
Taiwan	National Health Insurance Administration	National Health Insurance Administration	Pharmaceutical Benefit and Reimbursement Scheme (PBRS)	National Health Insurance Administration
UK	National Health Service (NHS)	National Institute for Health and Care Excellence (NICE)	NICE	Patient Access Scheme Liaison Unit (PASLU)

- **Administrative body.** The decision-making agency is the administrative body in charge of health insurance or prices in each country, e.g. The National Health Service (NHS) in the United Kingdom, the Federal Joint Committee (Gemeinsame Bundesausschuss/G-BA) in Germany, the French National Union of Health Insurance Funds (Union nationale des caisses d'assurance maladie/ UNCAM) in France, and the Central Social Insurance Medical Council in Japan (Chuikyo).

- **Evaluation agency.** The evaluation agency is a dedicated agency affiliated to the government or established with grants from the government, e.g. the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Pharmaceutical Benefits Advisory Committee (PBAC) in Austria, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/IQWiG) in Germany, the Transparency Committee (CT) and the Economic and Public Health Assessment Committee (CEESP) in France and the Health Insurance Review & Assessment Service (HIRA) in Korea.

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- **Evaluation expert group.** The evaluation expert group is convened by the evaluation agency, and its members are mainly experts recommended by professional academic institutions or associations and also include personnel employed by the evaluation agency. In addition, auditing of some dossiers submitted by manufacturers may be entrusted to professional research institutions.

- **Voting agency.** The voting agency votes on whether a drug can be listed according to the results provided by the evaluation agency. The voting agency is established by the decision-making body, and its members are relatively representative with a certain tenure in office (figure 6). A drug may be listed only if more than half of the voters vote in the affirmative. Generally, the list of voting representatives and the voting results will be disclosed, but the specific vote of each representative will not.

  – The Transparency Committee (TC) of France has 28 representatives with voting rights including specialists, general practitioners, pharmacists, patient representatives and statisticians [4].The Economic and Public Health Assessment Committee (CEESP) of France has 33 representatives with voting rights, which would theoretically consist of 1/3 economists, 1/3 public health experts (public health experts, epidemiologists, doctors) and 1/3 sociologists and anthropologists[5].Representatives of both TC and CEESP are to serve for three years and may serve for up to two consecutive terms.

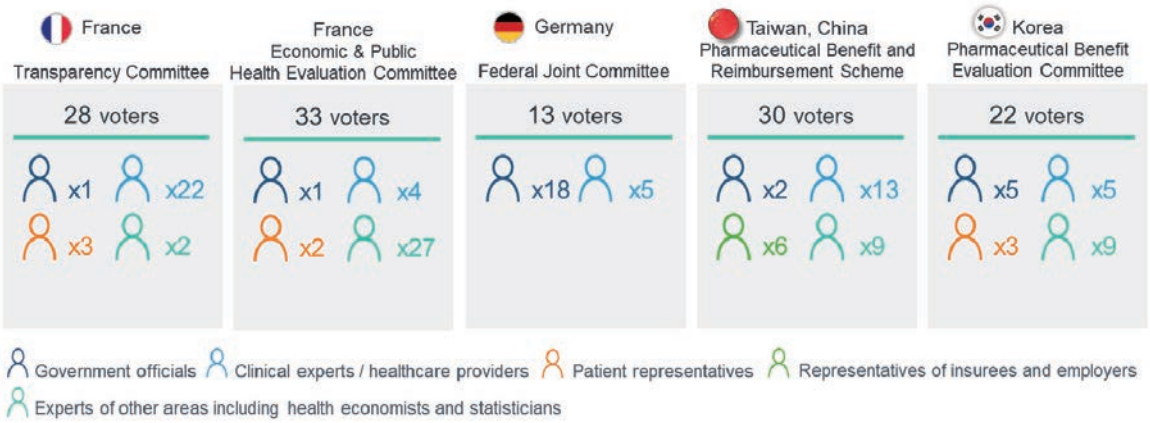
  – The Plenum of the Federal Council of Germany (G-BA) is composed of 13 voting representatives[6] including three independent members and representatives from the four leading organizations in the German health system[7] : the Federal Health insurance Fund Association (GKV-SV), the German Hospital Federation (Deutsche Keramische Gesellschaft e.V./DKG), the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung/KBV) and the National Association of Statutory Health Insurance Dentists (Kassenzahnärztliche Bundesvereinigung/KZBV) have nominated five, two, two and one representative, respectively, each with a six-year term in office[8].

Reference to International Practice

– In Taiwan, the Pharmaceutical Benefit and Reimbursement Scheme Joint Committee that determines the drug listings and payment prices has 30 representatives with voting rights, including one representative from the National Health Insurance Taiwan Administration (NHITA) and one from the Taiwan Food and Drug Administration (TFDA), nine experts and scholars (including at least four with medical specialty backgrounds), three representatives of insured persons, three representatives of employers and 13 representatives of medical service providers[3].The tenure of office is two years and may be renewed upon expiration.

– The Pharmaceutical Benefits Committee under the Health Insurance Review & Assessment Service (HIRA) in Korea has 22 representatives, including 13 permanent representatives from HIRA (3), the Ministry of Food and Drug Safety (1), the Ministry of Health and Welfare (1), patient populations (3) and pharmaceutical associations (5); in addition, nine flexible representatives are randomly selected from 58 academic experts[9].

Fig.6 Examples of the constitution of voting members



- **Negotiation agency.** The agency participating in negotiation on behalf of payers is usually independent of the evaluation agency. For example, price negotiations are conducted by the French Economic Committee for Health Products (Comité économique des produits de santé/ CEPS) in France, by the National Association of Statutory Health Insurance Funds (GKV-SV) in Germany and by the National Health Insurance Service (NHIS) in Korea; in Australia, the Department of Health has directly undertaken work concerning PBS drug price negotiations since 2014; in Canada, price negotiations are conducted provincially, and the Pan-Canadian Pharmaceutical Alliance (PCPA) is responsible for, on behalf of each province, joint negotiations with pharmaceutical manufacturers for setting prices of branded drugs. Negotiators sign confidentiality agreements upon participation and have ample time to review reports issued by health technology assessment agencies.

Procedure for the implementation of negotiation-based inclusion of innovative drugs

The current procedure for negotiation-based inclusion of innovative drugs to the NRDL comprises of seven steps: identification of drugs for negotiation, invitation for negotiation and dossier submissions, expert evaluation, pre-negotiation communication between government and manufacturers, negotiation and price agreement, signing of contracts, and publication of results. Since the basic framework has already taken shape, it is suggested that the procedure be continually followed and operating details be further improved.

I. Negotiation drug candidate selection

1.Submission of applications for NRDL listing

It is suggested that a channel for new drug applications be established for the dynamic NRDL update process, in which manufacturers submit the application form and standard dossiers to the evaluation agency. Based on the information in these submissions – as well as practical experience and information from other relevant sources -- the evaluation expert group assesses whether the drugs are innovative. Submissions for the NRDL may require the following materials:

(1) Application form (suggested word count: within 500 characters)

The applicant expresses its request to include a currently un-listed drug into the NRDL.

(2) Product dossiers

Qualifications, marketing information and clinical evidence of the product should be described, including:

- **Drug qualifications (suggested word count: within 2500 characters)**

The indications, pharmacology, clinical administration, efficacy, safety and patent status of the drug should be briefly described. Copies of the package insert and patent certificates should be attached.

- **Market information (suggested word count: within 2000 characters; information to be provided in table format)**

The number of eligible patients (nationally) in the recent three years, the annual sales amount, and the current ex-factory price should be presented in table format. Drug listings on provincial reimbursement lists should also be presented in table format.

- **Clinical evidence (suggested word count: within 5000 characters; information to be provided in table format)**

All clinical study results about the drug should be presented in table format, including published and unpublished clinical registration study reports and domestic and overseas literature. Studies on the list must be conducted with control groups, either placebo or blank controls. The clinical evidence list should include the following items:

- Quoted data sources and whether they have been published
- Research organizations, lists of investigators, study periods, sponsors
- Subjects, sample sizes and sources
- Therapeutic regimens in study groups and control groups
- Clinical endpoints
- Primary results

The full texts of study literature included in the list should be attached; if the registered clinical study report has not been published, the full text of the report should be attached.

2.Determine negotiation drug list

Since all drugs for negotiation are innovative drugs and are mainly used in top-tier medical institutions in large cities from clinical and pharmaceutical experience. Thus, it is advised that the review panel should mainly consist of clinical expert, pharmaceutical expert in top-tier medical institutions in large cities and academic leaders in corresponding treatment areas. And take academic leader in the corresponding field of therapy as the principle thing.

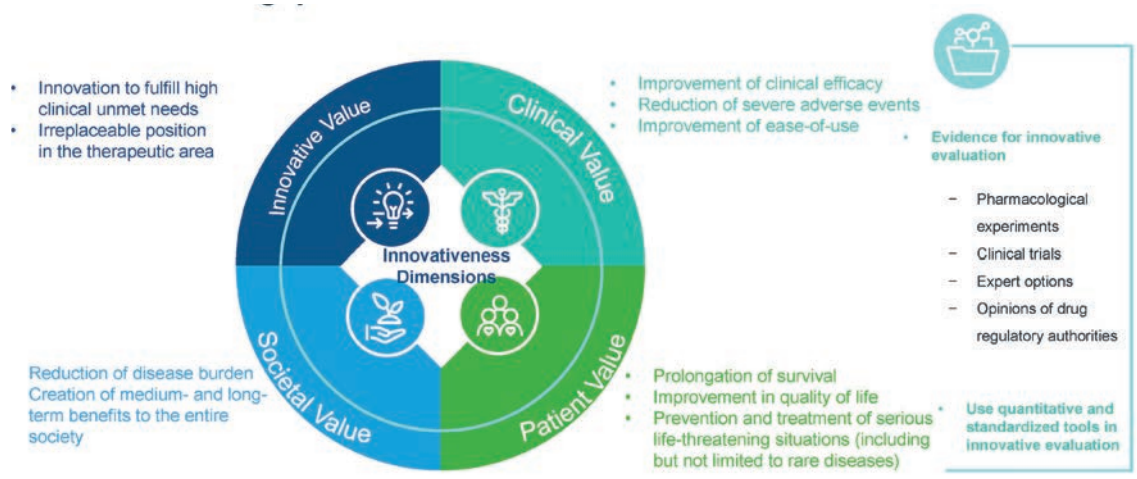
Innovativeness will mainly be evaluated by the new drug´s irreplaceability relative to those in the current NRDL or whether the drug will bring significant improvements to some indicators of critical concern. From the perspective of health insurance management in China, the innovative value of new drugs should be evaluated with respect to the following dimensions: (1) innovative value: if the drug´s mechanism of action meets an unmet clinical need and serves as an irreplaceable treatment; (2) clinical value: including improvements in clinical efficacy, reduction of severe adverse reactions, improvements in ease of use, etc.; (3) patient value: including prolonged survival, improvements in quality of life

Procedure for the implementation of negotiation-based inclusion of innovative drugs

focusing on but not limited to rare diseases and serious life-threatening situations; (4) social value: including reduction of disease epidemics, alleviation of disease burden, bringing overall benefits to society in the medium and long term, or promoting positive industry development by exploring innovation in mechanisms of action or other clinically significant scientific research on the basis of clinical and patient value.

Evidence for innovative evaluation should come from a variety of channels, including pharmacological experiments, clinical trials, expert opinions, etc. At the same time, the clinical value of new drugs should be evaluated by reasonably referencing the opinions of drug regulatory authorities during market review and approval of drugs. For example, the establishment of consistent "green channels" should be considered for clinically urgently- needed new drugs that have definite clinical value and are qualified for priority regulatory review (Fig.7).

Fig.7 Evaluation of Innovativeness of New Drugs and sources of evidence



Sources: desk research, IQVIA analysis

To comprehensively and accurately reflect the process of this expert evaluation, quantitative and standardized tools may also be employed, e.g. Delphi method was used to assign weights to the above indicators of innovation and conduct quantitative scoring, or by conducting quantitative analysis of primary observation endpoints (such as survival time, quality-adjusted life years).

Since the innovative value of new drugs would already be evaluated in clinical, patient, industrial and social dimensions in the first step, it is suggested that for the economic evaluation, the expert group should mainly consist of pharmacoeconomics and health insurance experts, and standardized and quantitative tools should be employed to measure the cost-effectiveness of new drugs scientifically. Pharmacoeconomic tools have been widely used in internationally to assist public health decision-making. Therefore, Incremental Cost-Effectiveness Ratio (ICER) can be used as a preferred indicator to scientifically evaluate the economic value of drugs, as it takes into account the clinical benefits and cost changes brought by new drugs. At the same time, when setting the government´s willingness-to-pay threshold, fairness and ethical considerations should also be accounted for, giving special considerations to effective drugs for rare diseases.

Reference to International Practice

In different countries and regions, the innovative value of drugs is usually considered from the following aspects: (1) clinical efficacy; (2) safety; (3) quality of life of patients; (4) economy; and (5) social benefits (unmet need for disease treatment, breakthrough in the action mechanism, etc.).

In Germany, additional benefits (e.g. values of innovation) of innovative drugs are assessed according to a six-level scale: level 1 (major additional benefit); level 2 (considerable additional benefit); level 3 (minor additional benefit); level 4 (additional benefit which is not quantifiable); level 5 (no additional benefit); and level 6 (the benefit is less than those of the comparator) [8,10]. Drugs at the first four levels are all referred to as "innovative drugs with additional benefits". For the first three levels, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/ IQWiG) performs evaluation for all-cause mortality, disease conditions and symptoms, adverse reactions and quality of life (Table 1) [11]. In addition, IQWiG uses the relative risks (RR) and odds ratios (OR) of relevant clinical outcome indicators and calculates their two-sided 95% confidence intervals to quantitatively determine the added value of drugs (Table 2) [11].

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Table 1 Germany Experience: Evaluation Criteria for Drugs with Additional Benefits

	Type of outcome indicators/patient-related outcomes			
Score of additional benefits	All-cause mortality	Disease conditions and symptoms	Adverse reactions	Quality of life
Major Additional Benefit	Major increase in survival time of patients	Long-term freedom from serious symptoms (or late complications)	Extensive avoidance of serious adverse events	Major improvement in quality of life
Considerable Additional Benefit	Considerable increase in survival time of patients	Alleviation of serious symptoms (or late complications) Considerable reduction in non-serious symptoms (or late complications)	Reduction in serious adverse reactions Considerable avoidance of other non-serious adverse events	Considerable improvement in quality of life
Minor Additional Benefit	Increase in survival time of patients	Statistically significant alleviation of serious symptoms (or late complications); Alleviation of non-serious symptoms (or late complications)	Statistically significant reduction in serious adverse events Reduction in other non-serious adverse events	Improvement in quality of life

Sources: desk research, IQVIA analysis

Table 2 Germany Experience: IQWiG Assessment of Drug Innovativeness

	Patient-related outcomes		
Score of additional benefits	All-cause mortality	Serious symptoms, serious adverse events and quality of life	Non-serious symptoms, non-serious adverse events
Major Additional Benefit	0.85	0.75 (risk≥5%)	n/a
Considerable Additional Benefit	0.95	0.90	0.8
Minor Additional Benefit	1.00	1.00	0.9

Sources: desk research, IQVIA analysis

Reference to International Practice

In France, the Improvement of the Medical Benefit (Amélioration du Service Médical Rendu/ASMR) with new drugs over existing regimens is mainly evaluated in terms of improvement in efficacy and improvement in tolerance and graded into five levels: level I, major improvement in therapeutic efficacy, e.g. major reduction in death rates of serious diseases; level II considerable improvement in therapeutic efficacy/tolerance; level III, moderate improvement in therapeutic efficacy/tolerance; level IV, minor improvement in therapeutic efficacy/tolerance; and level V, no improvement in therapeutic efficacy[12]. Drugs at the first three levels are considered to have certain innovative value, and their prices are set by referencing international prices; drugs at the last two levels are considered to (practically) have no innovative value, and their prices are set by referencing prices of domestic drugs of the same kind [13]. For drugs with level I-III ASMR categories self-evaluated by manufacturers and an annual budget impact of more than 20 million euros, manufacturers submit assessment dossiers to the Transparency Committee (TC) and also submit economic assessment dossiers to the Economic and Public Health Assessment Committee (CEESP) under HAS [14].

In Japan, the value of new drugs is evaluated mainly in terms of i.e. innovative value (improvement in efficacy) and market value (satisfaction of unmet demand), so as to determine the premium rate. A premium of 5-120% is allowed for the former, and a premium of 5-20% for the latter [15]. Innovative drugs in Japan are classified into three categories: innovative drugs without reference drugs, drugs with reference drugs but with considerable innovativeness, and drugs without considerable innovativeness. Drugs in the first category are priced based on their costs; drugs in the second category are marked up according to their efficacy and market values; and drugs in the third category are priced by referencing prices of drugs of the same kind [15]. Primary evaluation indicators for category 2 innovative drugs are listed in Table 3.

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Table 3 Japan Experience: Innovativeness Assessment of Drugs with Reference Products

Indicator	Definition	Premium
Innovativeness	All of the following conditions are satisfied: • New clinical action mechanism • Greater efficacy and safety than currently available drugs of the same kind • Improvement in treatment of identified indications	70-120%
Usefulness (1)	Two of the above 3 conditions are satisfied	35-60%
Usefulness (2)	One of the above 3 conditions is satisfied OR: • Production of greater benefits than currently available drugs of the same kind through compatibility improvement	5-30%
Marketability (1)	The following two conditions are satisfied: • The primary indication is a rare disease • No reference drug with similar prices has been included in the reimbursement list	10-20%
Marketability (2)	The following two conditions are satisfied: • The primary indication pertains to the "small market" in the "Japan Standard Commodity Classification" • No reference drug with similar prices pertaining to the "small market" has been included in the reimbursement list	5%
Pediatric drugs	The following two conditions are satisfied (pediatric clinical trials must have been conducted in Japan) • Developed for pediatric use • No reference drug with similar prices has been included in the reimbursement list Note: If both this category and marketability (2) are satisfied, the prices will be increased according to this category.	5-20%
Sakigake designation	All of the following conditions are satisfied: • New action mechanism different form all drugs currently available in Japan, America, the United Kingdom, Germany and France • Approval was obtained in Japan ahead of other countries • The drug will be marketed in other countries after launch in Japan • Conditions for usefulness (1) are satisfied	10%

In Taiwan, new drugs included into the coverage of national health insurance are categorized into class 1 new drugs and class 2 new drugs depending on innovativeness. Class 1 new drugs are breakthrough innovative drugs with considerable improvement in clinical efficacy. Class 2 new drugs are further categorized into class 2A and class 2B; the former are new drugs with moderate improvement in clinical values over the current best common comparators, and the latter are new drugs with clinical values approximate to those of reference drugs [16]. Class 1 drugs are priced by referencing the median of drug prices in the 10 reference countries; and class 2 drugs are priced by one method among the lowest

price in the 10 reference countries, the price in the country of origin, the international price ratio method and the course-dose ratio method, with the median price in the 10 reference countries set as the price ceiling [16].

In the United Kingdom, the value of innovative drugs is mainly evaluated in terms of acquirable quality of life, satisfaction of demands of special populations (e.g. rare diseases) and the impact on survival time of end-stage patients. In the United Kingdom, the incremental cost-effectiveness ratio (IECER) recommended by NICE is generally 20,000 and 30,000 pounds/QALY [17]. However, the access threshold may be elevated up to 50,000 pounds/QALY for end-stage diseases [17] and up to 100,000-300,000 pounds/QALY for special medical technology used in rare diseases [18].

II. Negotiation invitation and submission of dossiers

After undergoing the selection process, the health insurance authority will issue a negotiation invitation to manufacturers along with a list of submission materials required. In the recent three years of negotiation, the health insurance authority gave a relatively detailed list required for negotiations. Nevertheless, the details need further standardization and improvement based on existing templates. First, a relatively fixed submission template should be developed to define submission requirements in a clear and detailed manner. Second, manufacturers should be allowed to use relevant data held by the health insurance authority so that a consensus on essential data can be reached as early as possible. Third, the use of confidential information, such as confidential prices on foreign markets, should be avoided where possible. Fourth, for drugs that are expected to enter the negotiation process, manufacturer can apply to early communication with health insurance department. The main communication content include comparison, model selection, evaluation methods, etc. Fifth, clarify the review rule and measurement evidence of materials before submit the materials. At the same time, prior to formal negotiations, more face-to-face communication opportunities with the authority should be duly provided to manufacturers in an effort to effectively coordinate negotiation requirements at early stages.

After review by the Expert Advisory Group, additional evidence would need to be supplemented for the drugs pending negotiation to support economic evaluation. The supplementary dossiers should include the following contents:

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1.The supplementary dossiers should include drug qualification data, market information, clinical and economic evidence.

2.A systematic review of pharmacoeconomics (suggested word count: within 8,000 characters)

Manufacturers are strongly encouraged to submit a product-specific pharmacoeconomic systematic review, preferably including data from Chinese studies. This will help review experts carry out their reviews and strengthen the scientificity of negotiation evidences.

A control group for the pharmacoeconomic evaluation could be comparable durgs in NRDL, the original clinical standard treatment drugs and international III phase clinical research controlled drug, etc. If no suitable control drug is available, then a placebo control or a no-treatment control can be selected instead. The selected comparative product should have the same or similar therapeutic goal as the drug candidate, the latest treatment plan that has been included in NRDL, and try to avoid choosing less effective treatment regimen as control group.

The pharmacoeconomic evaluation method can be in the form of a cost-effectiveness analysis (CEA), a cost-benefit analysis (CBA), a cost-utility analysis (CUA) or a cost minimization analysis (CMA). It is recommended that a cost analysis or cost-benefit analysis be submitted as far as possible.

3.International and domestic price information (suggested word count: within 2,000 characters; information to be provided in table format)

Price information on the negotiated drug in designated countries or regions are to be listed in table format. The information should include the cost insurance & freight (CIF) price, ex-factory price, terminal sales price (indicating whether tax is included), market launch time, and the drug´s reimbursement status. The designated countries (regions) should include key countries (regions) with a universal healthcare insurance scheme. Prices in different parts of domestic should at least include the lowest and highest bid-winning prices nationwide, the bid-winning price in the province with the highest sales, as well as the converted daily costs, annual costs and costs per treatment cycle.

4.Pricing scheme recommendations for negotiations (suggested word count: within 2,000 characters)

Propose a potential price adjustment scheme, target population, treatment plan, and reimbursement payment standard recommendation.

5.Expected sales and budget impact on healthcare insurance funds (suggested word count: within 3,000 characters; to be submitted as a calculation sheet in EXCEL)

Assuming that the drug is selected for NRDL inclusion, an analysis should be conducted to forecast the number of target patients, total sales, total sales amount per year, and the possible budget impact on healthcare insurance funds in the coming three years.

Submissions for this section would also need to be supplemented by a budget impact analysis (BIA) calculation sheet in EXCEL; the BIA´s internal structure and calculation codes are required to be made available to users, allowing users to freely adjust key parameters and explore analysis results.

6.Possible new indications and off-label use (suggested word count: within 1,500 characters)
Reference to International Practice

Health technology assessment (HTA) agencies in different countries (regions) have published instructional documents for the application process as well as dossier submission requirement lists and templates, etc. to improve transparency and reduce manufacturer costs for dossier preparation.

The instructional documents for dossier preparation fall under two major categories. The first category mainly consist of guidelines for pharmacoeconomic research, specifying rules about the conduct of these studies. The second category includes the requirements list and formatted templates to be submitted to the health insurance authority. Instructional documents from both categories have been fully released by the assessment agencies in the United Kingdom, Canada, Australia, Germany, France and Taiwan (Table 4).

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Table 4 Overview of Application Submission Requirements in Selected HTA Countries (regions)

	UK	Canada	Australia	Germany	France	Taiwan
HTA agency	NICE	CADTH	PBAC	IQWiG	HAS	NHITA
Systematic review						
Systematic review for clinical studies	✓	✓	✓	✓	✓	✓
Quality assessment for the included clinical studies	✓		✓	✓	✓	✓
Systematic review for economic studies	✓				✓	
Quality assessment for the included economic studies	✓				✓	
Economic modeling						
Guideline for economic modeling	✓	✓	✓		✓	
Budget impact analysis (BIA)						
Guideline to BIA estimation	✓	✓	✓		✓	
BIA submission template	✓	✓	✓		✓	✓

Source: Desk Research, IQVIA Analysis

Sources: desk research, IQVIA analysis

III. Expert review

Expert review covers three aspects: quality of dossiers submitted by manufacturers; pharmacoeconomics (cost-effectiveness); budget impact on the healthcare insurance fund. The review group provides feedback, which includes pricing opinions.

1.Dossier quality review

Review experts will firstly review the quality of the dossiers submitted by pharmaceutical manufacturers to check whether the evidence submitted is scientific and authentic. The review group needs to review whether the dossiers submitted by pharmaceutical manufacturers conform to healthcare insurance regulations, and assess the quality of studies included in the systematic review. The review group also needs to verify the credibility of dossiers submitted by pharmaceutical manufacturers based on the information from other sources, and finally determine whether the dossiers submitted by pharmaceutical manufacturers are credible.

2.Cost-effectiveness review

Only the dossiers approved through quality review could be accepted for economic review. The expert group would review the economic aspects of drugs based on the dossiers submitted by pharmaceutical manufacturers and information from other sources. The preferred economic assessment indicator is the "incremental cost-effectiveness ratio" (ICER), which refers to the cost per quality-adjusted life year (QALY) gained.

If the QALY indicator is unavailable, clinical indicators can be considered as health output indicators, but it would still be necessary to establish the relationship between clinical indicators and quality of life, or between clinical indicators and therapeutic cost. When neither QALY indicator nor clinical indicator are available, a CMA can be presented for assessment. The calculated costs should consider (1) the substitution of the new drug on the original treatment plan and its impact on costs; (2) improvement of efficacy and its impact on treatment costs; and (3) reduction of adverse reactions and its impact on costs, etc.

3.Budget impact analysis

A BIA should also be conducted for negotiation drugs to analyze the expected impact on healthcare insurance funds. It is suggested to consider the actual use of doses and savings in direct medical costs in our country (e.g., reduced hospitalization and care costs due to disease progression). For drugs with significant budget impact, the expert group may raise proposals for considerations such as the scope of usage, price, healthcare insurance payment ratio, and payment method.

The expert review group should conclude with the review group´s final recommendations, including feedback on the quality of the dossiers submitted by pharmaceutical manufacturers and the economic evaluation of the drug and the advice about applicable people, price, payment, etc.

The review results should then be formatted to clearly present the recommendations.

Among the expert group´s recommendations, the price is often the focus of attention for all parties. Therefore, a clear price decision basis and rules should be established. Generally speaking, pricing can be achieved based on three aspects, the first aspect is economy review basis on cost-effectiveness, and concurrently considering evaluations from countries/regions such as the UK, Japan, and Taiwan

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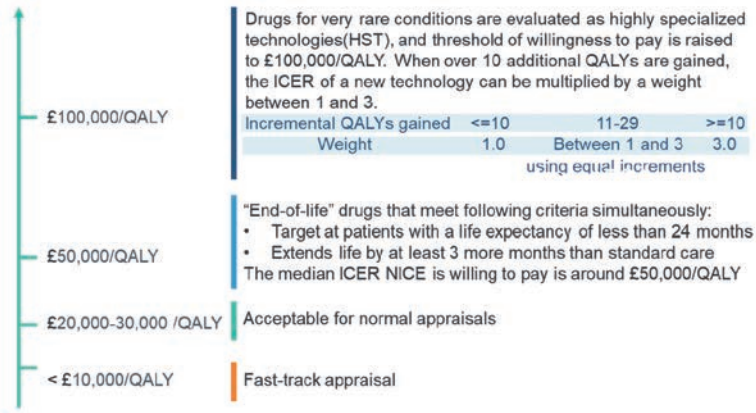
as reference. Other value dimensions may, for example, the treatment regimen with great public health value that can bring significant end-of-life value, reduce disease transmission and epidemics, Or for rare diseases, such as the lack of effective treatment for disease-related drugs to be comprehensively considered. The second aspect is basis on the effect for medical insurance fund, In the medical insurance fund expenditure threshold limit, forms the price. The third being the international reference price, which is often based on prices paid in other countries/regions that adopt universal health coverage. Besides the international reference price itself, multiple factors such as the number of indications and the reimbursement ratio need to be considered. When using the international reference price as a pricing tool, complex factors affecting the price in different countries should be further considered to determine a specific method to calculate external reference pricing. For high innovation level product, relax the standard of international reference price and take the arithmetic mean or median value. Three aspects form the basis for obtaining a price that is not necessarily the lowest as the suggested price.

Reference to International Practice

The United Kingdom´s NICE adopts a cost-effectiveness threshold for new drugs, which is generally a number between 20,000 and 30,000 per QALY. When the ICER calculated is less than 20,000 per QALY, the new drug would be considered as highly cost-effective and recommended for extensive use. When the ICER calculated is between 20,000 and 30,000 per QALY, the new drug is considered to be cost-effective in general and needs to be used in a limited manner. When the ICER calculated is more than 30,000 per QALY, the new drug is considered to be not cost-effective and needs to be strictly restricted in use [17]. In practice, the United Kingdom may relax the access criteria for a new drug that can greatly improve the QALY, prolong survival at the end of life and treat rare diseases. For example, for an end-stage disease with an expected life span of less than 24 months, if a new drug can extend the life by more than 3 months, then the access threshold can be raised to 50,000-125,000 per QALY [17] ; for ultra-rare diseases (target indication prevalence less than 1/50,000), the Highly-Specialized Technology (HST) evaluation model will be used and the access threshold can be raised to 100,000-300,000 per QALY [18].For a new drug that can significantly improve quality of life, the threshold may be no more than 100,000 per QALY if the incremental QALY is less than 10; the threshold may reach 100,000-300,000 per QALY if the incremental QALY is between 10 and 30; the threshold is 300,000 per QALY if the incremental QALY exceeds 30 (figure 8).

Fig.8 NICE'S threshold of willingness to pay for different new technologies



Unlike the United Kingdom, other countries have no clear-cut requirements on the cost- effectiveness threshold, but their general values can be estimated roughly according to the CEA results of the drugs recommended by their assessment agencies to their health insurance authorities. For example, in the last few years, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended C$50,000 per QALY as the mean value of ICER for drugs being covered by health insurance, suggesting that C$50,000 per QALY might be the general threshold considered by CADTH [19] . Likewise, the range of threshold considered by Australia´s Pharmaceutical Benefits Advisory Committee (PBAC) is estimated between A$45,000 and A$60,000 per QALY [20,21] and the ICER threshold of Health Insurance Review Agency (HIRA) in South Korea might double the per capita GDP [22].

France, Germany, Japan and Taiwan have set rules for calculating the incremental value and price. In France, the relationship between clinical-added value (ASMR) rating and drug price is provided in the framework agreement signed between the Economic Committee of Healthcare Products (CEPS) and the French Pharmaceutical Companies Association (LEEM) every three years. According to the 2016-2018 CEPS-LEEM framework Agreement [13] the negotiated price of a drug leveled ASMR I-III and approved by pharmacoeconomic assessment is no less than the minimum price in Germany, Spain, Italy and the United Kingdom; for a drug leveled ASMR IV, the lowest-priced drug referred is taken as the negotiated price; for a drug leveled ASMR V, the negotiated price should not be lower than the minimum price of all reference prices (including prices of generic drugs) [13].

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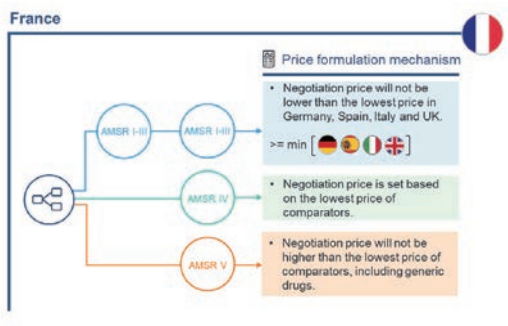
Reference to International Practice

In recent years, most new drugs have been leveled as ASMR IV-V, so France determined after negotiations in July 2018 that the minimum reference price is no longer taken as the only basis for drugs leveled ASMR V[23]. With respect to the drugs that are leveled ASMR I-III by manufacturers themselves and have an annual budget impact exceeding € 20 million in any year from the second year after being put on market, a CEA needs to be provided as one of the references for price negotiations [14].

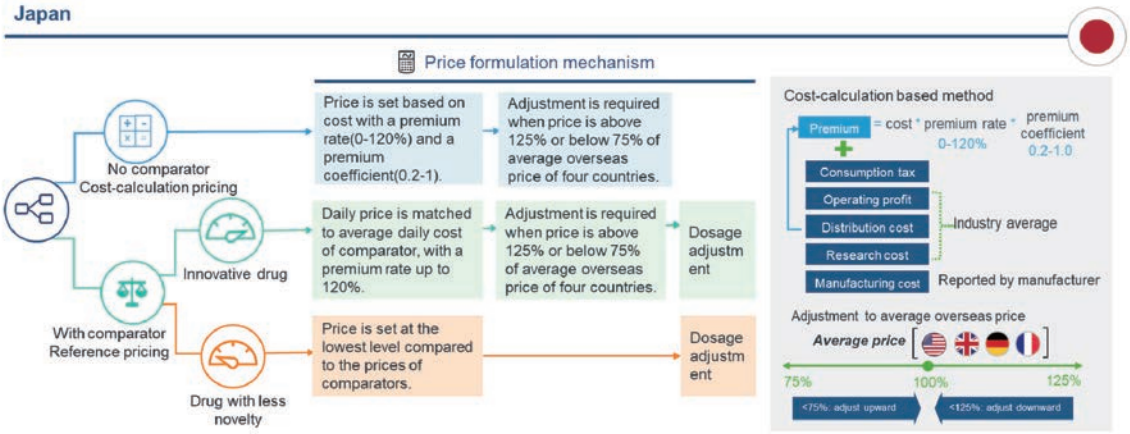
Fig.9 Illustration of drug price formulation in France



In Japan, innovative drugs are divided into three categories: innovative drugs without reference drugs, drugs with reference drugs but notably innovative, and drugs that are not notably innovative. Among them, innovative drugs without reference drugs are priced by means of cost-based pricing, which means using production costs plus reasonable profits and expenses to set the price. When it comes to cost-based pricing, manufacturers are required to provide complete and detailed cost-related information, including all costs incurred in the production and sales links and the number and time of labor involved in the production process. The pricing agency mainly refers to industry standards to check and assess the production costs of manufacturers. Industry average coefficients (the coefficients are regularly released by the Development Bank of Japan, or the Economic Affairs Division of the Health Policy Bureau under the Ministry of Health, Labor and Welfare based on results of industry surveys and researches) can be referred for adjusting part of the costs or profits. The price may also fluctuate within the operating profit margin of -50% to +100% according to the degree of innovation, effectiveness and safety of the drug. For innovative drugs with reference drugs but notably innovative, the price is

added based on the value assessment results. Finally, the price is adjusted by referring to international reference prices (lower the price if it´s 1.25 times higher, raise the price if it´s 0.75 times lower) and specifications [15] . Japan applies the arithmetic mean value of the retail drug prices in the US, the United Kingdom, Germany and France to determine the international reference price. For innovative drugs that are not notably innovative, the minimum price is set by comparing it with the prices of similar drugs in the last few years, and then adjusted by referring to the international reference price (no more than 1.25 times).

Fig.10 Illustration of drug price formulation in Japan



Reference to International Practice

Taiwan also has more transparent rules for the formation of healthcare insurance payment prices, which are helpful for manufacturers to pre-judge the prices. When it comes to a new drug of the first category (breakthrough and innovative drug), pricing is based on the median price of the drug in ten countries (the United Kingdom, Germany, Japan, Switzerland, the US, Belgium, Australia, France, Sweden and Canada). In Taiwan, when the clinical trials reach a certain scale, 10% can be added to the price [16] For a new drug of the second category, one of the following methods can be selected for the pricing with the median price of the drug in above-said countries as the upper limit. According to clinical value improvement, the method selected for pricing can be the minimum price of the drug in these ten countries, price of the drug in the original country, international drug price proportion, or dose proportion

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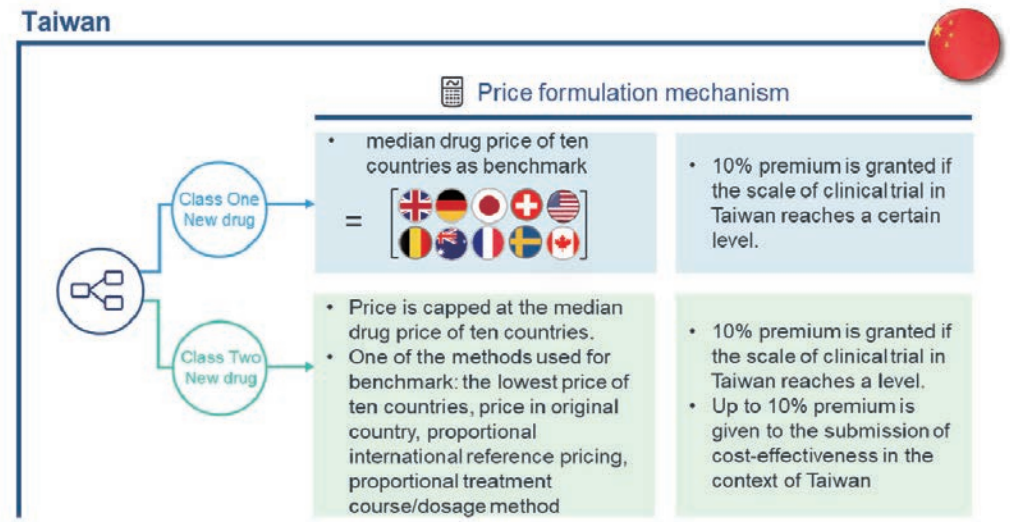
in a course of treatment. Generally, the minimum price obtained through different pricing methods is taken as the benchmark. In Taiwan, if clinical trials are carried out locally and reach a certain scale, 10% can be added to the price. When submitting the pharmacoeconomic assessment, a maximum 10% premium can be added [16]. Currently, Taiwan focuses its pharmacoeconomic assessment review on whether the method applied is reasonable and whether the setting of parameters reflects the actual conditions of Taiwan, not on the ICER value. In actual practice, the added proportion is somewhere between 4% and 6%.

Fig.11 Illustration of drug price formulation in Taiwan



IV. Pre-negotiation communication

In order to facilitate the two negotiating sides to reach a consensus on drug-related evidence, the suggestion is to have a communication channel between the review agency and the manufacturers. As such, the manufacturers would have the opportunity for answering questions raised in the expert review, supplementing new dossiers, and/or responding to feedback from expert review.

This communication mechanism already exists for current negotiations on innovative drugs, there are some suggestions to improve the communication and normalization of feedback process. First, the expert´s recommendations should be written in formatted documents, allowing manufacturers to have a clear understanding of the expert opinions. Second, expert recommendations should list specific questions that need to be addressed by the manufacturers, and provide opportunities for adding supplementary explanations or evidence. Third, if a manufacturer´s supplementary explanations or supplementary evidence are adopted, the review experts should modify the review opinions. In the end, the expert´s review opinions should be taken as an important basis for finalizing the preset government reservation price for negotiations.

Reference to International Practice

Internationally, there have been extensive discussions about improving the transparency of the review process. It is generally believed that the rules [24] to be followed include: (1) review rules are transparent and stakeholder engagement processes are open and transparent; (2) establishing a mechanism for reconsideration of review results; (3) maintaining openness and transparency between the review results and the final decision on health insurance access; (4) ensuring government transparency regarding the priorities of technology assessments.

V. Negotiation stage

During the negotiation process, the current negotiation rules allows the manufacturer to make two offers. If both offers are 15% higher than the preset government reservation price, the negotiation fails. Otherwise, the negotiation enters further discussion until an agreement on the price is accepted by both parties. In this situation, the negotiation team of the health insurance authority has the greater advantage. Since manufacturers have no idea what the preset reservation price is, they risk proposing offers that may already be lower than the preset government reservation price, which would then result with further lowering of the price. At this point, the negotiation price would be greatly affected by human factors of the negotiation team. Some negotiation groups may force down the price to a very low level, which may not be conducive to protecting the enthusiasm for pharmaceutical innovation in the long run. It is suggested that the negotiation expert allows the negotiators to give clear price hint

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to lead negotiations to a conclusion. To avoid the situation that the price is too low duo to differences between negotiation groups, setting a minimum transaction price protection mechanism in order to get a more stable result, for example, set the lowest price not less than 15% of the base price. If the price declared by the enterprise is significantly lower than the price recommended by the expert group, it is suggested that the price declared by the enterprise should be the payment standard of the medical insurance after being examined and approved by the administrative organization of healthcare security, and no negotiation should be conducted. In 2019, the negotiations attempted to engage in competitive negotiations, which accelerated the rapid decline of patented drugs in the absence of generics. It is suggested to carefully evaluate and adopt competitive negotiation for similar innovative drugs with the same indications.

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Reference to International Practice

According to a Korean study, South Korea´s 2007-2013 National Health Insurance System (NHIS)-negotiated price further dropped by 13.1% compared with the suggested price upon completing its HTA[25]. In terms of the price formation mechanism, Japan applies the external reference prices with the price range between 0.75 times and 1.25 times of the average of prices in the US, the United Kingdom, Germany and France to ensure that a reasonable price range is given[15].

VI. Contract signing

In 2017 and 2018, the contract procedure for state-level innovative drug negotiations is rather simple, namely a simple price contract publicly released. However, more forms of contracts for innovative drug negotiations are available for reference in international and Chinese local practices, may help to achieve the price, even keep the price confidential. Please see the following examples:

- Volume-based contract: The two sides under negotiation set a total quantity of drugs to be used within a certain period of time. If the actual quantity of drugs used exceeds the previously set quantity, then the price of the excess quantity should be appropriately lowered. Such contracts can avoid excessive impact on the health insurance fund and prevent manufacturers from over-promoting drugs.
- PAP: For every patient, a drug can be covered by health insurance or paid by the patient for a certain period of time, and then offered free of charge by the manufacturer for a subsequent period of time. Such contracts can promote greater profitability for the manufacturers under the premise of ensuring their original interests.
- Risk-sharing contract: All costs are paid for clinically effective cases, but the costs are exempted or discounted for ineffective cases. This can also be expressed by total efficiency. For instance, when efficiency reaches a certain level, all costs are paid; otherwise, costs are discounted. Such contracts require the availability of clear-cut indicators to reflect clinical efficacy.

The three types of contracts above can enable risk-sharing between the health insurance authority and the pharmaceutical manufacturers as well as allow manufacturers to have better expectations for the market environment. At the same time, such contracts help keep the price confidential, have little impact

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on the market price, assist manufacturers with safeguarding the international market price, and promote their participation in negotiations.

In 2019, negotiation encourage enterprises to propose the standard of intended payment under the risk sharing mode. Different contract forms include volume price linkage (gradient price reduction), pay-per-effect and pay-per-head schemes. But it was not considered as insufficient preparation time and implementation difficulty. It is suggested that communicate the risk sharing plan with the enterprise in advance, giving the enterprise enough time to prepare and negotiate with the negotiation experts.

In addition, it is suggested that the conditions for renewal of the contract, as well as the price change mechanism and exit mechanism of renewal should be agreed in the contract signed during the first negotiation. For example: (1) Establish the linkage mechanism of actual consumption and forecast consumption difference and reserve price determination during the contract period; For varieties with multiple indications, it is suggested that the actual dosage during the contract period should be counted based on the indications specified in the contract, and contract with the enterprise to communicate the impact of the fund budget statistical caliber and calculation logic when signing the contract; (2) Establish a mechanism to continue to discuss the extension of indications for varieties, allowing the addition of indications and adjustment of payment criteria during the term of agreement; (3) Establish continue discussion product´s exiting mechanism, the exiting includes two aspects: 1. if certain conditions are met, such as after the contract period, if the total amount of varieties does not exceed the expected total sales amount at the time of negotiation or if the reduction rate of 10-15% is met, it will be automatically included into category B reimbursement of medical insurance; 2. during the contract period, if the new real world evidence shows that the efficacy and safety do not achieve the expected effect, or the influence on the medical insurance fund is too large, and the price does not reach the equilibrium point between the two parties in the further negotiation, the gradual withdrawal mechanism can be adopted. (4) For the renewal varieties, it is suggested to simplify the submission materials and negotiation process in order to save negotiation resources; (5) For products that provide further evidence of real-world clinical or economic benefits, consider maintaining the original payment criteria; (6) Considering the factors of product life cycle, maintaining reasonable and stable profit is helpful for enterprises to invest in innovation continuously.

In addition, for drugs that fail in the negotiation, it is suggested that the healthcare security department establish a communication mechanism with enterprises to clarify the reasons for the failure, and supplement relevant materials to explain, so as to avoid repeated attempts.

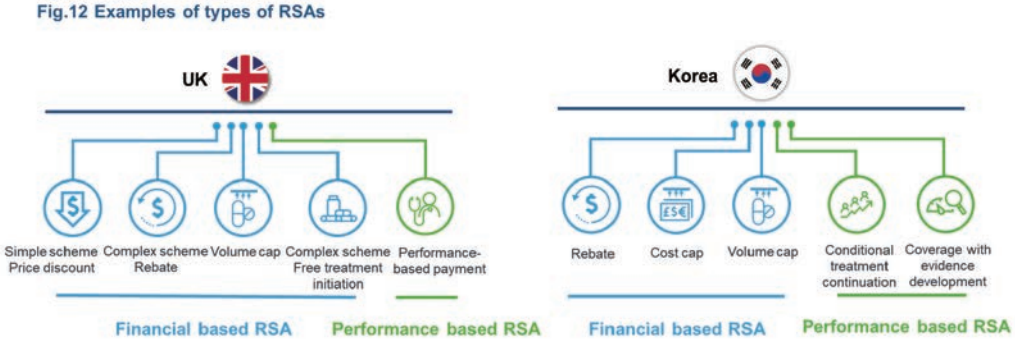
Reference to International Practice

In the United Kingdom, Germany, Australia, Canada and Taiwan, the price is directly made public if it is set based on the value assessment rules without the need for the insurer and the manufacturer to sign additional contracts. If the price needs to be further discounted or various risk-sharing mechanisms need to be implemented, the two parties need to enter into an agreement and keep the price confidential.

In the United Kingdom, negotiations on the "Patient Access Scheme (PAS)" are carried out with pharmaceutical manufacturers based on results of pharmacoeconomic analysis. The negotiation contract can be divided into direct price discounts and more complex risk- sharing, including reimbursement, upper limit of usage, and efficacy-based payment, etc [26] Public data show that, as of December 2018, 136 of the 156 PAS (87%) that are made public on the website of NICE are the form in which manufacturers sign confidentiality agreement on price discount with the government [27].

In December 2013, South Korea started to include oncology drugs or orphan drugs for major diseases without other treatment options and other drugs deemed necessary for price negotiations in the scope of implementing the risk-sharing agreement. Up to now, five modes of risk-sharing agreement have been proposed, including Refund, Expenditure Cap, Utilization Cap/Fixed Cost Per Patient, Conditional Treatment Continuation + Money Back Guarantee, and risk-sharing contract[28]. By Q1 of 2018, 26 drugs had been listed through various forms of agreements in South Korea. These drugs are concentrated in treating oncology and rare diseases and most of them are listed through such types of agreements such as Refund and Expenditure Cap[29].

Fig.12 Examples of types of RSAs



Procedure for the implementation of negotiation-based inclusion of innovative drugs

VII. Public release of results

Currently, only the final negotiation price is announced for national healthcare insurance negotiation; the review opinions on dossiers submitted by manufacturers and the main basis for pricing are not made public. In order to improve the fairness and transparency of government decision-making and to enhance social credibility, disclosing the expert´s review opinions and the main basis for pricing in an appropriate form (except for confidential contents) may be considered; publishing the list of review experts in appropriate time is also an option for strengthening the accountability mechanism. For the varieties of negotiated payment standards that apply for confidentiality, the relevant departments shall not publish their payment standards in open channels during the term of the agreement, and the price shall not be displayed in the drug trading system.

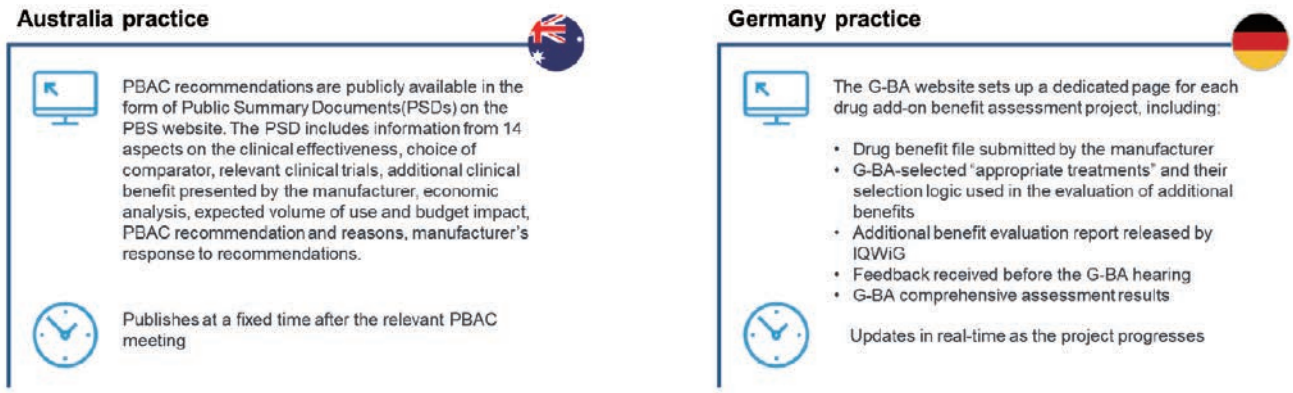
Reference to International Practice

In countries (regions) being taken as references in this study, the HTA review opinions for a new drug are usually made public in a timely manner in the form of documents. In the United Kingdom and Australia, the review opinions disclosed mainly include the assessments of clinical value, economic value and evidence quality of a drug submitted by the manufacturer, social, ethical, and other considerations, and recommendations based on the evidence submitted. In Australia, the documents released by the Pharmaceutical Benefits Advisory Committee (PBAC) are relatively comprehensive, and fall under 14 parts. These 14 parts consist of the application purpose, approval status, indications and limitations, clinical usefulness, reference selection, related clinical trials, manufacturer´s self- proven clinical added value, economics, estimated usage and budget impact, PBAC´s review opinions and reasons, the manufacturer´s reply to the review opinions, etc[30].

If a risk-sharing agreement is signed, the actual price covered by health insurance is generally not disclosed to the public. Looking at the practices of the United Kingdom and Australia, publicized results will disclose whether the health insurance authority has signed the risk-sharing agreement as well as the type of agreement with the manufacturer, however the price of the drug actually paid by health insurance under the risk-sharing agreement is hidden. At the same time, clinical trial information that has not been publicly disclosed in the submitted materials, and the information in the pharmacoecomomic model that can be used to infer the actual payment price of health insurance will also be hidden.

After the German Institute for Quality and Efficiency in Health Care (IQWIG) completes the preparation of a review report, G-BA releases it on the official website. Within a specified period of time, G-BA accepts feedbacks from the manufacturers, the academic community and the society. The feedback should be filled in the template required by G-BA and supported by the full text of the corresponding research literature. The feedback should be submitted online via the website of G-BA or via email, and the submitter can register for participating in corresponding hearings held by G-BA[31].

Fig.13 Forms of recommendations to be disclosed



Key issues that need to be addressed in the implementation of innovative drug negotiations

The NRDL update (including negotiations on innovative drugs) involves health, finance, pharmaceutical supervision, industrial and many other departments. Therefore, the smooth implementation of negotiations on innovative drugs requires inter-departmental consensus and information sharing, and coherence in policies on drug price, purchase and usage. In addition, the implementation also requires d the establishment of a special agency for dynamic NRDL updates (including negotiations on innovative drugs).

Inter-departmental information sharing & strengthening the establishment of basic data on the healthcare system

Negotiations on innovative drugs require the support of data from multiple sources, which need the sharing of information among departments. These data include: (1) data about drug safety and efficacy from the regulatory department; (2) data about drug innovation from the industrial sector and the regulatory department; (3) reasonable medication suggestions and data about essential drug selection from the health department; (4) data about the drug use status from medical institutions.

At the same time, the establishment of a public health information system should be further strengthened at the level of overall planning and top-level design to promote national- level health insurance data management and the informatization of medical and health institutions at all levels. The medical and health big data quality management mechanism of medical and health data s hould be established as soon as possible. Relevant supporting laws and regulations should be promulgated to promote the process of standardizing medical big data in an environment in which healthcare big data is increasingly more widely used in the field of public decision- making.

Promotion of negotiation results implementation

For the purpose of timely implementing the outcomes of negotiations on national health insurance access, policy coordination among relevant departments and the coordination between central and local health insurance policies are needed. After the negotiation in 2018 and 2019, the Health Insurance Agency is associated with the Health sector published document for the implementation of negotiation

drug, most of questions has been resolved, the implementation of negotiation drugs has been accelerated. However, there are some operational details can continue to improve:

1.The contract period negotiated is the market exclusivity period. The term of contract should be suggested reasonably by referring to international common practices and domestic bidding contract, and raise reasonable contract period. The negotiated term of contract is two years in general, or more than 2 years. For new drugs with generic or alternative medicines are expected to be available within two years, it could remain the stipulation that the state adjusts the medical insurance payment standard according to the situation of imitation products on the market.

2.Within the validity period of the contract, if a new indication is approved to benefit more patients, the enterprise may submit an application for extending the limit of payment.

3.The price policy upon the expiration of the negotiated contract should be made clear. After the negotiated contract expires, the price of the negotiated drug that is still within the patent term is suggested to be adjusted proportionately by referring to the price changes of reference products or the price changes in the reference markets. For the negotiated drug that is no longer within the patent term, the reimbursement standard should be set by referring to the price of clinically substitutive products.

4.Increasing the innovative drugs accessibility. Part of varieties have high storage cost in the hospital, thus, the hospital unwilling to store these drugs in the hospital pharmacy. It is suggested to draw on the experience of some cities, setting up a "double channel" in each city and include it in the payment of medical insurance funds. And considering appropriately increasing the reimbursement rate and the ceiling line.

5.Real-world, evidence-based healthcare decisions and policy review mechanisms should be strengthened. As the efficacy and safety of a new drug require a process of constant review, the suggestion is to emphasize the use of real-world evidence for the efficacy and safety based on Chinese patients while assessing the access to health insurance reimbursement. Considering to maintain or raise original payment standard for the drug which can provide further evidence of real-world clinical or economic benefits.

key issues to be addressed in negotiation implementation

Support for the development of value assessment technology

Value assessment is the core technology applied in negotiations on innovative drugs. The health insurance authority may develop the technical standards for economic assessment and the format of assessment reports applied in health insurance negotiations according to the economic evaluation guidelines or technical standards released by current professional institutions.

Value assessment also requires the support of some basic conditions, including epidemiological data, disease progression patterns, quality of life of patients with different states of disease, data on costs of different treatment options and so on and so forth. The health insurance authority should coordinate relevant departments in the provision of information and support some basic research to acquire the basic information required in value assessment.

Organizational capacity building

After initiating the dynamic NRDL update mechanism, negotiations on innovative drugs will become regular practice, meaning a rather stable and specialized institution will be required to undertake these responsibilities. According to international practices, this role will be performed by a specialized, independent, third-party accredited agency established by the government. Such agencies include IOWiQ in Germany, NICE in the United Kingdom, PBAC in Australia, and CADTH in Canada.

Review agencies play an important role in organizing, coordinating and supporting the negotiation and evaluation of innovative drugs. The review agency may set up an expert group or entrust a professional organization (such as a university or a research institute) to review the dossiers submitted by pharmaceutical manufacturers. In addition, it is necessary to establish the avoidance and punishment mechanism of experts or institutions providing relevant consulting services for enterprises.

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