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China on the Move: Lesson from China's National Negotiation of Drug Prices in 2021

In December 2021, China's National Healthcare Security Administration (NHSA) published the 2021 National Reimbursement Drug List (2021 NRDL), implementing greater pricing discounts than those seen in 2020.

This GT Advisory explores the following considerations:

- Out of 117 drugs negotiated, 74 were successfully added to the 2021 NRDL, including 67 with exclusivity. In comparison, 119 were successfully added to the 2020 NRDL. The average price cut of the 67 drugs is 61.7%, higher than 50.64% in 2020.
- Domestic companies are responsible for the majority of newly added medicines, and some multinational companies still struggle to strike a deal with NHSA for their oncology products.
- Just as in 2020, seven orphan drugs were included in the 2021 NRDL. However, the reimbursed products could not come close to their prices in other countries, and some saw a 95% price cut in the negotiation.
- The "Dual Channel" regime offers a new path to distribute NRDL-listed drugs and may result in distribution channel reform on the pharmacy side.
- Consideration of budget impact became more prominent in the 2021 NRDL negotiation, and NHSA appeared to use the annual cost threshold as a dealbreaker.

- NHSA's so-called "soul bargaining" approach gained support from the Chinese public. This may cast an unfavorable light on the pharmaceutical companies that failed to reach an agreement with NHSA over its reimbursement decision.
- Non-Chinese pharmaceutical companies, especially bio-ventures, face greater challenges with fewer straightforward options to enter the Chinese market. Companies planning product launches will need to incorporate legal and policy developments early.
- Succeeding in China requires early and in-depth readiness. Preparation of market access concurrently with regulatory filing; early alignment in price negotiation across headquarters, regional, and local offices; and timely incorporation of insights into deal proceedings are important elements.

2021 NRDL Shows Dominance of Domestic Companies and Uncomfortable Discount Rate of 61.7%

The price negotiation between NHSA, the payer of China's public health care security system, and pharmaceutical companies was completed Nov. 12, 2021. NHSA published the 2021 version of the National Reimbursement Drug List (2021 NRDL) Dec. 3, 2021, effective as of Jan. 1, 2022. The procedures for NRDL adjustment, including the issuance of the adjustment plan on June 30, 2021 (2021 Working Plan), the formal negotiation, publication of final results, and the effective date of the new version of the NRDL, is earlier this year than in 2020. This could be the practice in coming years, as workflow in 2020 was largely delayed by the COVID-19 pandemic.

NHSA reportedly received 501 applications involving 474 drugs, and 271 drugs passed the preliminary review. NHSA's website published a breakdown of those 271 drugs, disclosing information such as generic names, market authorization holder names, indications, if any patent disputes existed, dosage, and description of effectiveness and safety. However, only 117 drugs were included in the negotiation in early November 2021. The CAR-T product, Yescarta (axicabtagene ciloleucel) of Fosun Kite, costing about 1.2 million per injection, was included on the short list but did not enter the negotiation. In contrast, Spinraza (generic name: nusinersen) of Biogen, which costs about RMB 700,000 for a single injection and treats the rare disease spinal muscular atrophy (SMA), was included in the 2021 NRDL despite failing in the past.

Out of 117 drugs negotiated, 74 were successfully added to the 2021 NRDL, including 67 with exclusivity. In comparison, 119 were successfully added to the 2020 NRDL. The remaining seven drugs were included as the generics of drugs in the prior NRDL. The average price cut of these 67 drugs is 61.7%, higher than 50.64% in 2020 and similar to 60.7% in 2019. "Soul bargaining" is the term used by Chinese media and internet users to describe NHSA's "gentle but firm" negotiation style. Of the drugs already included in the prior NRDL, 27 were renegotiated and remained in the 2021 NRDL, and 11 were excluded from the 2021 NRDL due to limited clinical value, significant substitutability, or low procurement volume. However, judging from the prices disclosed by NHSA, the prices of renegotiated products mostly remained unchanged.

As discussed in our January 2021 GT Advisory, more than half of the newly included western medicines on the 2020 NRDL were the products of multinational pharmaceutical companies. In 2021, on the other hand, domestic companies were responsible for the majority of newly included medicines. Hengrui had six newly included drugs (four as new products and two targeted drugs approved for new indications). BeiGene and Betta each had one product included in 2021 NRDL, while Pfizer had three newly included products and Roche and Gilead each had two.

1. Multinational Companies Struggle to Strike a Deal with NHSA for Oncology Products

There are currently four types of domestic programmed cell death protein 1 (PD-1) products listed in the 2020 NRDL: Innovent (Sintilimab), Hengrui (Camrelizumab), Junshi (Toripalimab), and BeiGene (Tislelizumab). Before June 30, 2021, all of these products were approved for new indications. Sintilimab and Tislelizumab each had three new indications, and Camrelizumab and Toripalimab each had two. Two other domestic players joined the competition in August 2021: Penpulimab by Akeso and Sino Biopharmaceutical, and Zimberelimab by Gloria and Wuxi Biologics. According to NHSA, only drugs whose approvals (as new drug or new indication) were granted earlier than June 30, 2021, were qualified as candidates of NRDL adjustment this year. Therefore, the competition mainly focused on new indications of the four domestic products. Innovent, Junshi, and BeiGene's new indications are included in the 2021 NRDL, yet Hengrui's two indications are not, which may be attributed to its worse-than-expected financial performance in the third quarter of 2021.

Just as in 2020, none of the imported PD-1 products, i.e., Keytruda of Merck Sharp & Dohme (MSD), Opdivo of Bristol-Myers Squibb (BMS), and Durvalumab of AstraZeneca, were listed in the 2021 NRDL.

In recent years, antibody drug conjugates (ADC) have received widespread attention in the medical industry. Among the three approved ADCs (Trastuzumab Emtansine of Roche, Brentuximab of Takeda, and Disitamab of RemeGen), only RemeGen's product, the first domestic ADC (approved for certain gastric cancer in June 2021), is included. In fact, both established pharmaceutical companies and new biotech companies are competing to develop new generations of ADCs. Quite a few ADCs are under clinical study, from companies like Hengrui, Fosun, RemeGen, Lepu, and others. Everest Medicines has already filed a new drug application for its product Sacituzumab Govitecan. Following the current crowded PD-1 product market, the ADC category may constitute the largest portion of the next wave of oncology product launches in China.

2. Certain Orphan Drug Included in 2021, but Company Must Lower Price Below Certain Annual Cost Threshold

NHSA has been working to ensure patient access to orphan drugs (i.e., pharmaceuticals that remain commercially undeveloped owing to limited potential for profitability) by leveraging its bargaining power as well as market competition. NRDL applies to all provinces in China, so drug inclusion must account for the provincial balance of public health insurance. Prior to the 2021 NRDL, critical illness insurance in Zhejiang, Shandong, and other provinces covered several rare diseases. Since 2020, local governments initiated cooperation with commercial insurance to promote "inclusive commercial insurance." As a general principle, coverage of anti-cancer drugs take priority over rare-disease drugs. For example, the Shanghai inclusive commercial insurance (Huhuibao), applicable to citizens insured by the city's basic medical insurance, covers 13 types of cancers and three types of rare diseases (including Fabry disease).

Seven orphan drugs were included after the 2020 negotiation, largely alleviating economic pressure on patients. Spinraza of Biogen for SMA was not included for failure to reach an agreement on price concession with NHSA. In 2021, another seven orphan drugs were added to the NRDL, including Biogen's two products Spinraza for SMA (six injections in the first year, and about three injections the following year) and Fampridine, which treats multiple sclerosis. Biogen reportedly cut the price of Spinraza to about RMB 30,000 (around $4,800 USD) per injection (a 95% discount). Additionally, Fampridine is the only drug approved for walking dysfunction among MS patients, differentiating it from Gilenya and Mayzent of Novartis (included in NRDL in 2020).

Takeda had two products for rare diseases included in the 2021 NRDL: Alglucosidase alfa (which costs about RMB 1 million per year) for Fabry disease and Icatibant for hereditary angioedema. Both drugs were approved in early 2020.

Another drug included in the 2021 NRDL but not included in the 2020 NRDL is Pfizer's Vyndamax (generic name: Tafamidis). Currently, there is no substitute for Vyndamax approved in China. However, Pfizer offered an up to 60% price cut on volume-based procurement websites in several provinces in early and mid-2021 at which time Vyndamax was already covered by inclusive commercial insurance in a few cities.

Outside China, Spinraza competes with Roche's Risdiplam (approved in China in June 2021) and Novartis's Zolgensma (approved in the United States in 2019, under clinical study in China). In the United States, Zolgensma costs over USD $2 million for a single injection, which Novartis says remains effective for the patient's lifetime. Risdiplam's advantages are its oral administration and weight-related dosages; its annual cost varies from RMB 300,000 to RMB 1,000,000 in China. If Spinraza can create a reimbursement approach similar to that of orphan drugs, Zolgensma and Risdiplam may face pressure from NHSA to implement significant price reductions. Because of the competition between drugs in the same category or therapeutic area, NHSA has leverage in its negotiation with Zolgensma and Risdiplam, and Spinraza's price may be driven down in its next price negotiation in 2023.

3. NHSA Continues Improving Foundation of NRDL's Success

Interim Measures for the Administration of Use of Drugs Covered by Basic Medical Insurance (Interim Measures), published July 30, 2020, specify the standard procedure of annual NRDL adjustment, as well as criteria for inclusion and exclusion of drugs on the NRDL. Therefore, the 2021 Working Plan is similar to the Working Plan for the Adjustment of the 2020 NRDL (2020 Working Plan). However, with NHSA furthering the reform of public medical insurance, the following developments call for attention:

- **"Dual Channel" regime offers a new path to distribute NRDL-listed drugs and may result in distribution channel reform on the pharmacy side.**

The dual-channel regime, introduced in May 2021, helps to address the time gap between when a drug is listed on the NRDL and when it is procured by a medical institution, caused by medical institutions' rigorous procurement procedures. Under the dual-channel regime, for drugs in the NRDL with high clinical value, urgent clinical need, and low substitutability, patients may purchase them in qualified retail pharmacies, in addition to medical institutions, with the same reimbursement ratio under local public medical insurance. NHSA gave provincial governments the power to formulate a catalog of drugs subject to dual-channel regime. Most provincial governments have issued local catalogs and implemented measures to establish the dual-channel regime. For example, four PD-1 products—Camrelizumab, Toripalimab, Tislelizumab, and Deutetrabenazine, which treat Huntington's Disease—are included in the dual-channel regime catalogue of Hunan Province, a province in central China.

According to NHSA, retail pharmacies within dual-channel regimes should adopt strict-quality drug-assurance measures and should be equipped with the delivery capacity to transport the drugs (such as injections that must be used in medical institutions) to medical institutions free of charge. In addition, pharmacy maintenance of electronic prescription systems is essential as a way to avoid insurance fund.

The dual-channel regime may boost the development of large-scale chain pharmacies, as small businesses may be less inclined to invest capital and personnel to meet the necessary requirements. In addition, patients may have more sources of drug procurement and pharmaceutical companies may have more

access to the end-user market. Specifically, pharmaceutical companies may be able to quicken their product rollout by bypassing hospitals and going straight to pharmacies.

- **Subsequent drug price adjustment in 2021 NRDL becomes more straightforward.**

According to the Interim Measures, if a generic drug is approved within the agreement period of brand-name drugs on the NRDL, the payment standard under medical insurance may be adjusted in reference to the pricing of such generic drug, or the generic name may be placed in volume-based procurement. That is to say, even if a brand-name drug has been included in the NRDL at a negotiated price, such price might be further lowered to the level of its generic equivalent launched in the agreement period.

When publishing the 2021 NRDL, NHSA announced that if a generic drug is approved or enters the volume-based procurement within the agreement period of drugs included in the NRDL, provincial governments may adjust the payment standard under medical insurance for the drug. Therefore, the price adjustment mechanism is more straightforward. The launch of generic drugs may lead directly to further price cuts, despite the significant discount conceded in NRDL negotiation.

From 2020 to 2021: Clearer Definition of Product Launch Environment in China for Non-Chinese Companies

A previous GT Advisory on the 2020 NRDL suggests (1) market access should be prepared earlier than or at least concurrently with the regulatory filing; (2) price negotiation success means an early alignment across headquarters, regional, and local offices; (3) these dynamics should be closely monitored and insights should be quickly incorporated into the deal proceedings. These considerations remain relevant. However, the 2021 NRDL negotiation further clarifies the Chinese pharmaceutical landscape:

- **Consideration of budget impact becomes more prominent.**

The 2021 NRDL negotiation consists of four steps: (1) clinical evaluations and recommendations by physicians and pharmacists; (2) calculation of reference insurance payment figures; (3) budget impact assessment on public health funding; and (4) opinion summary on the coverage cost targets and conditions by NHSA. The final NRDL list and inclusion criteria appear to establish a hard cap on the annual cost of treatment and to push pharmaceutical companies to make the largest concessions.

- **Public image of pharmaceutical companies.**

Since publication of the 2021 NRDL, there has been significant discussion of how NHSA negotiators pushed the pharmaceutical company representatives to lower prices, including at least one instance where the pharmaceutical company representative called headquarters for approval. Several television shows analysed how and why NHSA could negotiate with the pharmaceutical companies successfully, and most importantly, NHSA's fight for patients' best interests. NHSA's "gentle but firm" negotiation style captured in the public image can cast an unfavorable light on the pharmaceutical companies whose drugs were not included in the 2021 NRDL. Further, dramatic discounts on drug prices could imply that pharmaceutical companies ordinarily overcharge their patients for medication. As a result, there is a growing sentiment in China that pharmaceutical companies, especially foreign ones (which develop most high-priced treatments in China) are to blame for the lack of access to innovative drugs.

With the negotiation process in China made public, some payers in other countries are questioning the pharmaceutical companies' commitment to local patients, and current geopolitical tensions may further complicate the final considerations. For example, Chinese flagship biotech company BeiGene priced

Brukinsa (zanubrutinib) at RMB 99 ($16 USD) in China and $117.50 USD in the United States, a more than seven-fold increase. On Sept. 30, 2021, after three months on the market, BeiGene reported $33.7 million USD in sales of Brukinsa in the United States, slightly higher than its $32.1 million USD in Chinese sales. This result aligns with the price difference between the two countries. Pharmaceutical companies selling high-priced drugs may struggle to justify the value of their innovations.

- **Non-Chinese pharmaceutical companies, especially bioventures, face greater challenges.**

Increased operational costs in clinical development and distribution, national security considerations, technology transfer practices in manufacturing, and one of the lowest prices in the key pharmaceutical markets all contribute to the greater profitability of Chinese companies in China over multinational or non-Chinese companies. Perhaps the robust capital market and favorable financing environment in China established by various policies in the past compensate pharmaceutical companies enough. Most multinational or non-Chinese companies are hardly beneficiaries of the favorable financial environment directly. The outcome of these policy initiatives may encourage non-Chinese companies, especially small bioventures, which are currently responsible for the highest number of approved drugs by the U.S. FDA, to seek more collaborations with their Chinese peers for entry into China. This could further strengthen Chinese companies' competitiveness and accelerate the internationalization of Chinese companies. These developments align with the Chinese government's vision for the future, as reflected in China Vision 2025.

Moving forward, non-Chinese pharmaceutical companies may need to take a more creative approach when entering the Chinese market, incorporating legal and policy developments at an earlier stage in the planning process.

Authors

This GT Advisory was prepared by:

- Chia-Feng Lu ‡ | +1 202.331.3184 | +81 (0) 3.4510.2200 | luch@gtlaw.com
- Dawn (Dan) Zhang | +86 (0) 21.6391.6633 | zhangd@gtlaw.com
- John Gao | +86 (0) 21.6391.6633 | gaoj@gtlaw.com

‡ Admitted in The District of Columbia and New York. Not admitted in Japan.