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Value assessment and market access of innovative biologics in China

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1 Background

2 Value Assessment

3 Reimbursement Management

I. Innovative Biologics Industry Flourishes

CDE has established Priority Review and Conditional Approval to speed up the market launching of clinically urgent and effective drugs

- The number of innovative biologics approved by CDE is increasing, and exceeded 20 in 2017

Table. 2013-2017 The Number of Innovative Biologics Approved by CDE

Opdivo、Keytruda

- Blockbuster PD-1 drugs nivolumab and pembrolizumab both were approved through Priority Review.
- Nivolumab marketing approval takes **226** days
- Pembrolizumab marketing approval takes **164** days

II. The Importance of Innovative Biologics is Prominent

Table. Top 15 be

Severe disease such as cancer

10 of 15 are Innovative Biologics

Ranking	Generic Name (Brand Name)	Manufacturer	Indications	Classification	Sales (10^9$)
1	adalimumab（Humira®）	AbbVie	Rheumatoid arthritis	Biologics	184.27
2	rituximab（ Mabthera®）	Roche、Biogen	Non-Hodgkin's lymphoma, CML, etc.	Biologics	92.38
3	Lenalidomide（Revlimid®）	CELG	Multiple myeloma	Chemical	81.87
4	etanercept（Enbrel®）	Amgen、Pfizer	Rheumatoid arthritis	Biologics	78.85
5	trastuzumab（ Herceptin®）	Roche	HER2 breast cancer	Biologics	74.41
6	apixaban（Eliquis®）	Pfizer、BMS	Deep vein thrombosis and pulmonary embolism	Chemical	73.95
7	infliximab（Remicade®）	Johnson、Merk	Crohn's disease	Biologics	71.52
8	bevacizumab（Avastin®）	Roche	Metastatic rectal cancer	Biologics	70.96
9	rivaroxaban（Xarelto®）	Bayer、Johnson	Venous thrombosis	Chemical	65.89
10	aflibercept（Eylea®）	REGN、Bayer	Macular degeneration, macular edema, etc.	Biologics	60.34
11	insulin glargine（Lantus®）	Sanofi	Diabetes	Chemical	57.32
12	Prevnar13®	Pfizer	Pneumonia vaccine	Biologics	56.01
13	pregabalin（Lyrica®）	Pfizer	Neuropathic pain	Chemical	50.65
14	nivolumab （Opdivo®）	BMS	Melanoma, NSCL	Biologics	49.48
15	pegfilgrastim（Neulasta®）	Amgen	chemotherapy-induced neutropenia, etc.	Biologics	45.34

III. The Availability of Innovative Biologics is Unsatisfactory

Table. Some Important Biologics' Lowest Bid Price in China

No.	Generic Name (Brand Name)	Indications	Specification	Lowest Bid Price (￥)	Annual Treatment Cost (10^4￥)
1	adalimumab (Humira®)	Rheumatoid arthritis	0.8 ml:40 mg	7620	15~20
2	etanercept (Enbrel®)	Rheumatoid arthritis	25 mg	2030	6~8
3	rastuzumab (Herceptin®)	HER2 breast cancer	20 ml:440 mg	7600	10~12
4	infliximab (Remicade®)	Crohn's disease, RA	0.1 g	5180	8~10
5	cetuximab (Erbitux®)	Colorectal cancer, metastatic rectal cancer, head and neck cancer	20ml:0.1g	3805	15~20

China's Per Capita Disposable Income was RMB 25,974 in 2017, and Poverty Caused by Illness still exists.

In order to improve drug accessibility, innovative biologics should be evaluated scientifically and be included into the Medical Insurance.

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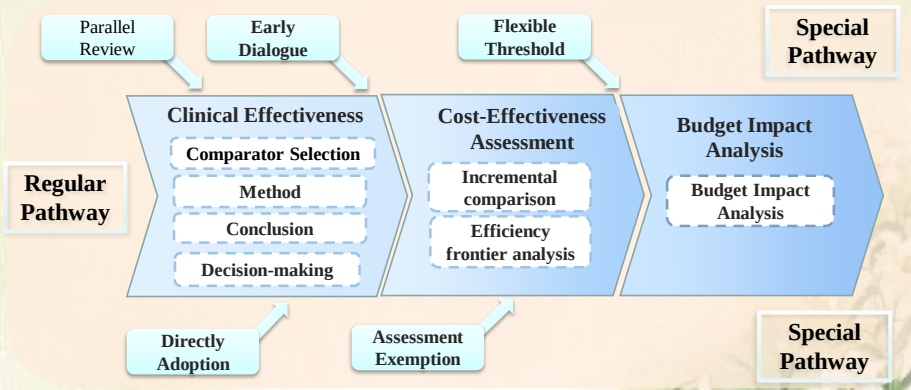
Value Assessment Mechanism

- Reimbursement decision-making based on scientific assessment is a global trend.
- For breakthrough innovative biologics, have set up special pathways to promote it's affordability.



I. Clinical Effectiveness Review

Registration Access	Reimbursement Access
• The balance of clinical benefits and risks • Safety 、efficacy	• added therapeutic value compared to comparators. • Relative safety、Relative effectiveness

- Clinical effectiveness review is the basis of value assessment.
- The review focus on added therapeutic value compared to comparators.
- In global perspective, it can be divided into pre-review (France、Germany) and simultaneous review (UK.)

I. Clinical Effectiveness Review

Comparator Selection

- Government-leading: the reimbursement access management agency set comparator selection criteria
- Selection Criteria : the same indication ; widely clinical used ; Official agencies have evaluated its cost-effectiveness

Review Method

- Enterprise report review : The data authenticity, the program scientificity, the results reliability
- Independent Evaluation: Systematic Review, Meta-analysis

Review Conclusion

- Evaluate the added therapeutic value by comparing with comparator

Decision-making

- According to the level of added therapeutic value, the related-decision can be divided into direct access, restricted access and negotiation access

I. Clinical Effectiveness Review—Regular Pathway

Review Conclusion

- Evaluate the added therapeutic value by comparing with comparator
- The added therapeutic value are usually expressed in drug levels:
  - Major improvement
  - Modest improvement
  - Minor improvement
  - No improvement

Table. Overview of the use of added therapeutic value

Countries	The added therapeutic value (ATV) classification levels
Belgium	Class 1: added therapeutic value Class 2:analogous or similar therapeutic value Class 3：generics/copies (same active ingredient)
Austria	①No added benefit（generics ） ②Similar therapeutic benefit ③Added therapeutic benefit for a subgroup ④Added therapeutic benefit for the majority ⑤Important added benefit for a subgroup ⑥Important added benefit for the majority
France	ASMR: I: Major improvement, II: Significant improvement, III: Modest improvement, IV: Minor improvement, V: No improvement
Germany	Added Benefit： ①Considerable additional benefit, ②Significant additional benefit, ③Small additional benefit, ④Additional benefit but not quantifiable, ⑤No evidence of additional benefit, ⑥Less benefit than comparator

I. Clinical Effectiveness Review ——Special Pathway

Parallel Review

- For breakthrough innovative biologics, HTA agency begins to evaluate drugs before its marketing approval.
- Regulatory agency shares the review data with the HTA agency .

How to get assessment data

1. Collect data in advance and ask companies to submit information
2. The assessment data and report shared by EMA's CHMP could be available for the HTA agency before the European Commission's final decision come out

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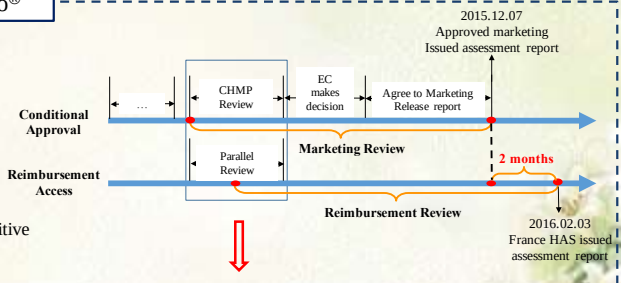
I. Clinical Effectiveness Review ——Special Pathway

Parallel Review

Case Study：Blincyto®

BLINCYTO (blinatumomab)

- **Brand Name：** Blincyto®
- **Company：** Amgen
- **Indications：** Philadelphia chromosome-negative and positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults and children.



Before marketing approval , France HAS obtained the drug's review data and assessment report of CHMP and conducted parallel review

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I. Clinical Effectiveness Review—— in China

- In China, the clinical effectiveness evaluation mechanism has been established.
- In the National Medical Insurance access negotiation, clinical effectiveness evaluation is an essential part.
- The enterprise should submit a clinical effectiveness assessment report as the basis of the review; comparators' information, clinical guidelines, relevant reports and literatures, etc. are used as supporting materials.
- The effectiveness review results will be used as a basis for price negotiation.

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II. Cost-Effectiveness Assessment

- Cost-effectiveness assessment is the core procedure of Health Technology Assessment.
- Most HTA countries use cost-effectiveness assessment to control drug costs.

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II. Cost-Effectiveness Assessment ——Regular Pathway

Incremental Cost-effectiveness Ratio

$$ICERs = \frac{C_{sample} - C_{standard}}{E_{sample} - E_{standard}}$$

Introduce **cost-effectiveness(C-E) threshold (λ)** as external reference:

When ICER＜λ, consider the drug to be cost-effective ;

When ICER > λ, consider the drug not to be cost-effective.

①**WHO recommended threshold**：1~3 times GDP per capita/QALY

②**Chinese applicable threshold**：¥50,000~150,000/QALY

II. Cost-Effectiveness Assessment ——Regular Pathway

NICE use **empirical determination** to find thresholds, which make a retrospective analysis of past assessment results.

Table. The types and ranges of C-E thresholds in different co

Threshold type	Representative countries	Ranges or cap values of C-E thresholds
Explicit	United Kingdom	£20000/QALY~£30000/QALY
	Thailand	160,000THB/QALY
	South Korea	$20,000/QALY
Implicit	Netherland	€10,000-80,000/QALY
	Sweden	€80,000-135,000/QALY
	Belgium	usually no more than $92,314/QALY
	Australia	average around 69,900AUD/QALY
	Canada	20,000-100,000CAD/QALY
	United States	$50,000-$150,000/QALY

II. Cost-Effectiveness Assessment ——Special Pathway

Flexible C-E Threshold

- If the innovative biologics cannot meet the regular standard of economic evaluation, it could be evaluated by special pathways.

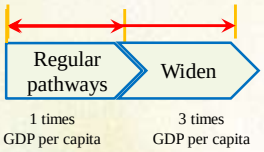

Table. C-E thresholds and flexible decision-making in different countries

Threshold type	Representative countries	Regular threshold	Flexible decision-making measures
Explicit	United Kingdom	£20,000/QALY -£30,000 /QALY	1）NICE raises the threshold for end-of-life drug **to £50,000/QALY ;** 2）Direct access for ultra-orphan drug when its thresholds **below £100,000/QALY**（Budget impact ≤ 20 million pounds）
	South Korea	$20,000/QALY (21,500,000KRW/QALY)	Use higher thresholds for severe cancer, rare disease and end-of-life patients: raise the thresholds for catastrophic disease, disease severity, no alternative, and limited alternatives. The average raising value is **17, 14, 12, 8 million KRW per QALY.**
Implicit	Netherlands	€10,000-80,000/QALY	Disease severity is one of the decision-making principles, **orphan drugs generally have higher thresholds.**
	Sweden	€80,000-135,000/QALY	The average access ICER value for severe disease is **€111,700/QALY**, for non-severe disease is **€79,400/QALY**
	Belgium	Usually below $92,314/QALY	Set the reimbursement ratio level according to drug necessity (disease severity is one of the influencing factors) : A(100%), B(75%), C（50%）,Cx（40%）,Cs（20%）

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Flexible C-E Threshold

UK

Regular C-E threshold : £20000-30000/QALY

End-of-life drug ：① Patients with a life expectancy that less than 24 months ；
② An extension to life of at least an additional 3 months compared with current NHS treatment.
The threshold for this kind of drug usually raises to **£ 50,000/ QALY.**

The assessment of *Kadcyla*® in UK

- **Generic name :** trastuzumab emtansine
- **Manufacturer :** Genentech
- **Indications :** HER2-positive advanced breast cancer
- **List price :** £1,641.01 for a 100-mg vial
- **ICER : £ 49,800/QALY**

Reimbursement decision :
NICE determined that *Kadcyla* meets the standard of end-of-life drug for treating HER2-positive advanced breast cancer. Therefore, NICE raised its threshold and made a **positive recommendation**.

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II. Cost-Effectiveness Assessment ——in China

- China has begun to explore the cost-effectiveness assessment and apply it to the National Medical Insurance access negotiation.
- According to local pharmacoeconomic report, pharmacoeconomic reports of other countries and the retrospective analysis report, the evaluation results will be used as the basis for the value assessment and price negotiation.

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Managed Entry Agreement

Managed Entry Agreement

Negotiation access → problem → Economic uncertainty; Clinical evidence uncertainty → solution → Financial-based agreement; Performance-based agreement

Financial-based agreement

- For drug with high economic uncertainty.
- **（1）Simple Discount agreement** provide discount to make ICER value meet the requirements.

（2）Price-volume agreement：price and volume are linked, control health insurance fund budget.

Financial-based agreement in Qingdao city

- **Brand name：** *Herceptin*®
- **Manufacturer ：** Roche
- **Indication：** Metastatic Breast Cancer

✓ In 2017, the co-pay patients number ceiling for *Herceptin* was 430. Exceeding the ceiling, Qingdao Medical Insurance Agency will not continue to pay.

Performance-based agreement

Performance-based agreement

- Breakthrough innovative biologics
  - Launch to market in a short time
  - Lack of real world data
  - Uncertainty around clinical evidence and adverse reaction
- It is necessary for payers to sign performance-based agreements in order to share risks.

1、indication severity
2、clinical uncertainty
3、data compensability

Sample size and Observation period

1 Applicable Conditions → 2 Agreement elements → 3 Data collection → 4 Reimbursement → 5 Agreement Transition

1、Assessment endpoint;
2、Assessment threshold;
3、Patient sample size;
4、Observation period ;
5、Compensation adjustment

Determine whether to reimburse the drug according to efficacy threshold

Agreement conversion

Fig. Performance-based agreement management process

Performance-based Agreement——in China

Zhejiang Province: Liver Transplantation reimbursement based on performance

- The medical expenses of patients receiving liver transplantation be reimbursed by Medical Insurance Agency according to the clinical performance.
- **Clinical performance indicator: life span after discharge**

Patients under the age of 18 years (including 18 years)

Objects	Performance Indicators	Proportion of Medicine Insurance Reimbursement
≤18 years	patients discharged from hospital	70%
	patients survived for over 1 year after discharge	20%
	patients survived for over 3 year after discharge	10%

THANKS!

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