Introduction and Process of the Pharmaceutical HTA in KOREA

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HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE

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01 Introduction of the Pharmaceutical HTA

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What is the Positive List System (PLS)

☞ **Positive List System = HTA introduction**

Definition

- System that grants benefits *selectively* to the drugs offering therapeutic excellence and high economic value (2007)

Objective

- To enable patients to use excellent drugs with optimum price by reimbursing cost-effective drugs
  → Ultimately, contributing to the improvement of people's health

Background of the PLS introduction

- (national context) implemented as a part of Korean Government's "Drug Expenditure Rationalization Plan (DERP)"

Why Did We Introduced the PLS (2007)

✓ ***Rapidly Rising Pharmaceutical Expenditure :*** ***29.2%*** *(2005)*
Key driving factor *of increasing Healthcare Expenditure*

Additionally , ***✓ Ageing population with Chronic diseases***
✓ Diffusion of New Technologies, New Medicine

Policy Action

"Drug Expenditure Rationalization Plan"

✓ ***Reform of the Reimbursement and Pricing System***
including Economic Evaluation, Price Negotiation (2007~)

Introduction of PLS

✓ ***Re-evaluation of the currently Listed****

Stepwise proceeded for 5 years including delisting (2007~2011)

✓ ***Additional Price Regulation Scheme for the Reimbursed***

Price-cut according to patent expiry and increase of the volume of sales

Goal

✓ ***Reinforce the Access to the Appropriate Medicine***
✓ ***Rationalize expenditure and Allocate limited resources efficiently***

* that were listed under the former regime of negative listing system

What are differences between NLS and PLS

Change of the National Health Insurance (NHI)'s Drug Listing System

	Negative List System (NLS)	Positive List System (PLS)
Reimbursement decision making process	After the MFDS's approval, - ***Almost all*** drugs* were automatically listed on the drug formulary for reimbursement * Except for approved drugs with statutorily not reimbursable indication	After the MFDS's approval, - ***Only reimbursable drugs*** that proven to be clinically and economically valuable are included on the formulary
Pricing	**① New drugs** - Relative Pricing Scheme (Referencing and calculating by ratio of domestic and foreign prices of the same therapeutics) - "Innovative" drugs : External referencing (7 countries) - Domestically developed new drugs : price estimation based on manufacturing cost	**① New drugs** - Reimbursement decision and pricing by conducting review of appropriateness of coverage and reimbursement price* and price negotiation** *Appraisal of the PBC – located at HIRA **NHIS
	② Generics Alternatives ≤ 80% of Off-patent drugs OR ≤ 90% of the Lowest generic drugs	**② Generics Alternatives** 68% of Off-patent drugs , from 6th generic, 90 % multiplied by order of entry ▶Off-patent drugs : 20% Price-cut

NHI : National Health Insurance, **MFDS :** Ministry of Food & Drug Safety,
HIRA : Health Insurance Review and Assessment Service **NHIS:** National Health Insurance Service

PLS Effects on the Drug Expenditure

Comparison of Drug price Before/After PLS

- **New drug price level compared to OECD countries[1)] (As of Jun 2014)**

PLS seems to contributes to lowering new drug price

	Before PLS	**After PLS**	Total
No. of Drugs	43	179	222
Price ratio (Korea / OECD average adjusted with PPP)	76.4 %	**62.1 %**	64.8 %

- **Limitation on the interpretation of result**
  - **lack of transparency in official drug price among foreign countries (Risk sharing agreement, discount, rebate, etc)**

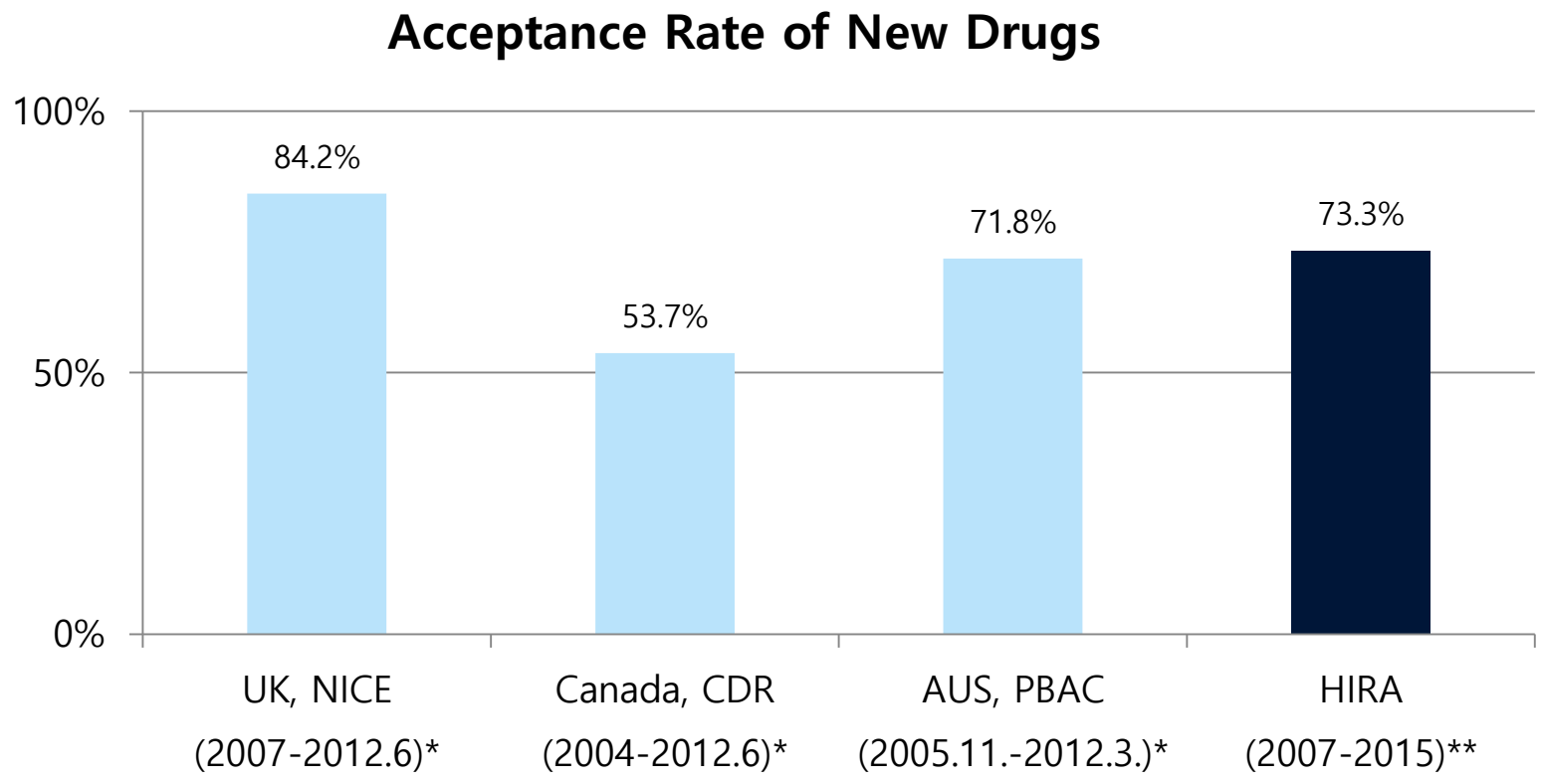
Global trends of decreasing transparency in drug price among foreign countries emphasizes the importance of value based pricing with local context rather than external referencing pricing

1) *Lee et al.* 2014

Pharmaceutical Benefit Decision Making

Access to Affordable Medicines After PLS

- International comparison to Acceptance rate

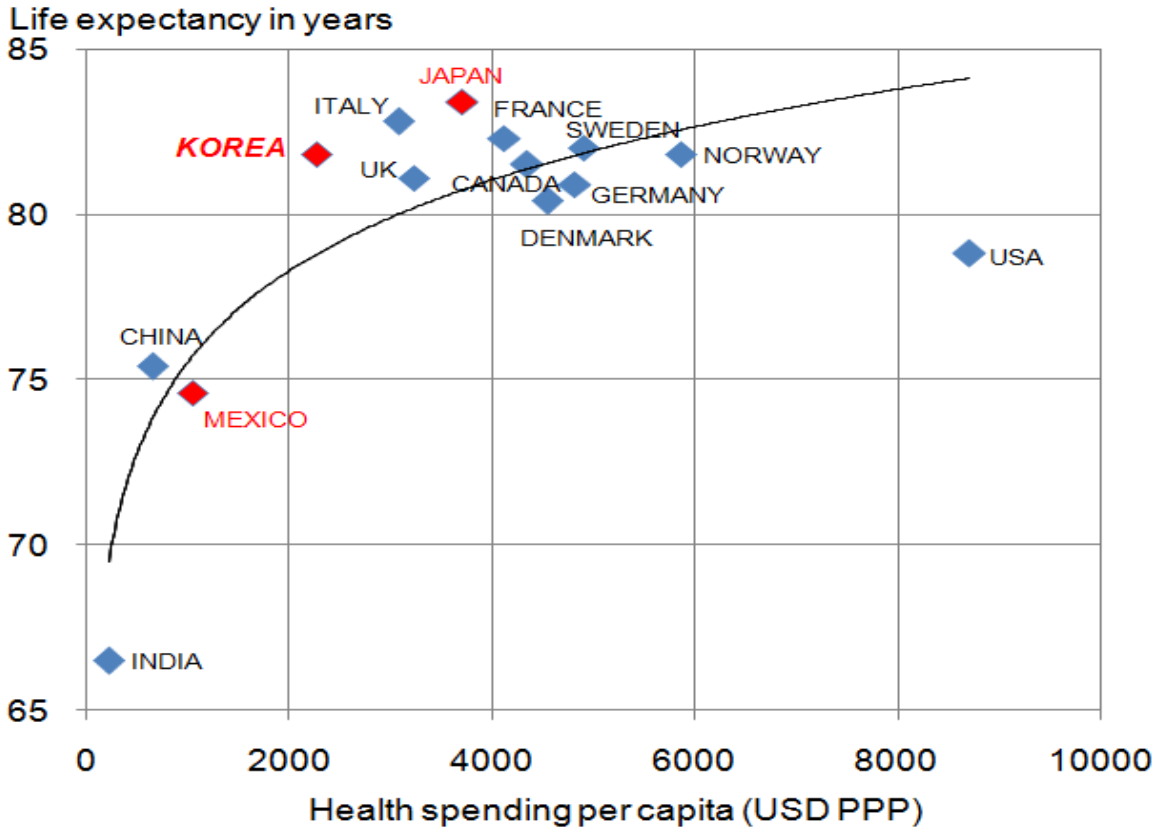


* Bae et al. (2013) ** HIRA Statistics

PLS Contribute to Health Performance

- **Korea has been achieving high performance with universal health coverage.**

Life expectancy at birth and Health spending per capita 2013 (or latest year)



Source : OECD Health Statistics 2015

PLS Impacts on Industry & Academia

Industrial Sector

- **Strongly opposed to the introduction of PLS in early phase**
  - Worries about the market withdrawal and price-cut
  - Negative effects on R&D and introduction of new drugs
- **Lacking Capacity to conduct economic evaluation**
- **Efforts to adopt to the new system and provide evidence for the assessment**

Academic Sector

- **Increase of the related researches**
  - In the social pharmacy field, master's and doctoral thesis on the topic of "economic evaluation" have increased 3.6 % (1999~2000) → 11.8 % (2007~2008)
- **Education of the manpower**
  - have developed educational curriculum for "economic evaluation" at graduate schools of public health, colleges of pharmacy, and relevant academic sectors
- **Perception on the performance of the PLS system**
  - Overall, positively view the system

PLS Challenges and Way Forward

- **Harmonization of**
  the fundamental principle of Selection and
  the NHI Benefit Coverage Expansion

- **Need to Discuss about Prioritizing for Public consensus**
  - **Societal thought on Willingness-To-Pay**
  - **Trade off among various factors considered in decision-making**

- **Outcome Research based on Real World Data(RWD)**
  - **After enlisting, Re-evaluation of high-price drugs (anticancer, orphan drugs) with RWD**

    - started in 2019 (pilot test)
    - review of clinical usefulness and cost-effectiveness
    - outcomes will be linked to drug price and benefit criteria

02 General Information on Drugs and Benefit Listing Procedure for New Drugs

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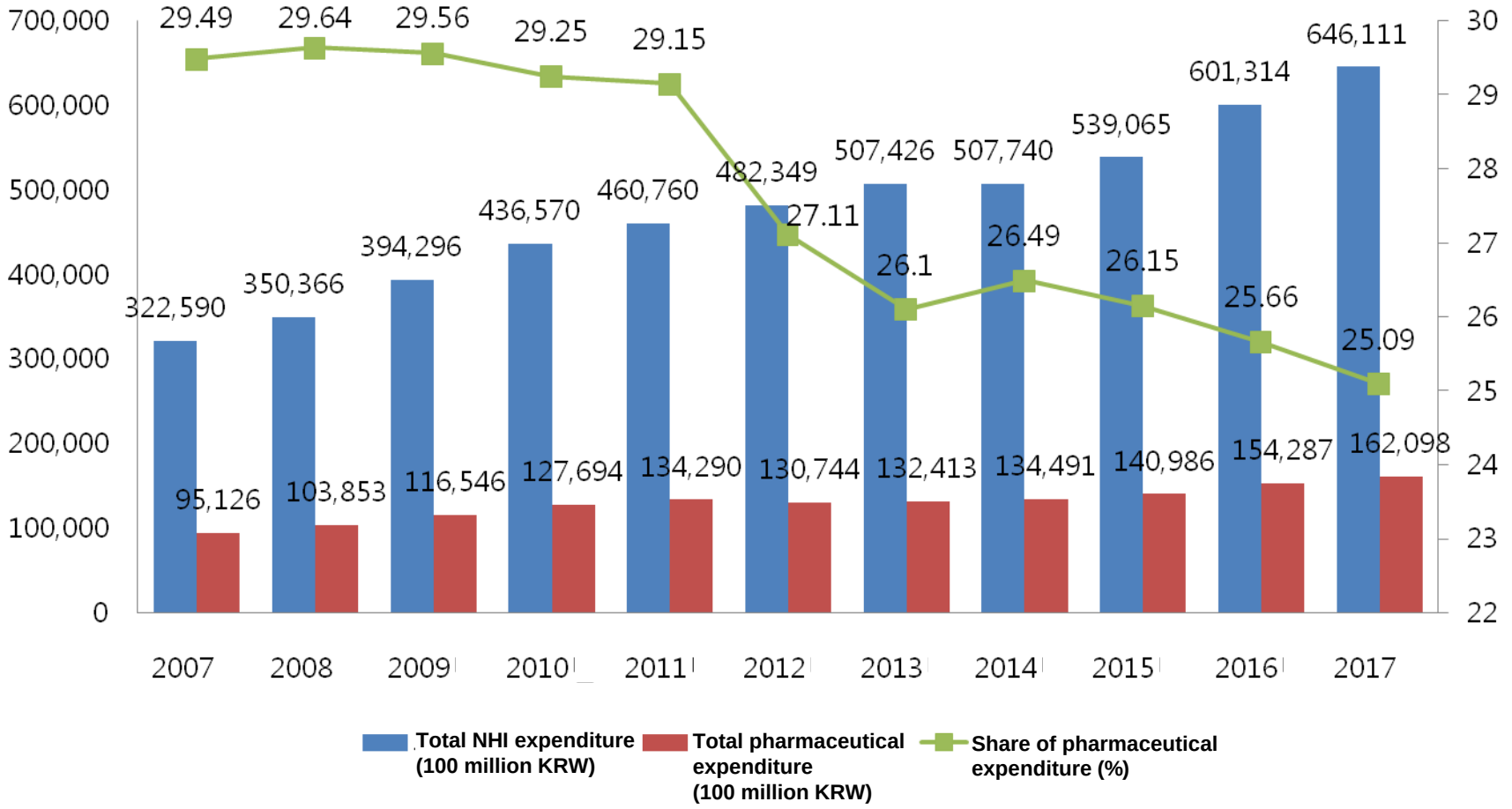
Drug Benefit Listing Status

Number of Drug Products on the Drug Benefit List

(Unit: number of drug products)

Year	Covered drugs			Uncovered drugs
	Total	Prescription drugs	OTC drugs	
Jan. 1, 2019	20,901	19,365	1,536	14,575
Jan. 1, 2018	22,389	20,493	1,896	14,248
Jan. 1, 2017	21,399	19,527	1,872	15,941
Jan. 1, 2016	20,401	18,458	1,943	15,309

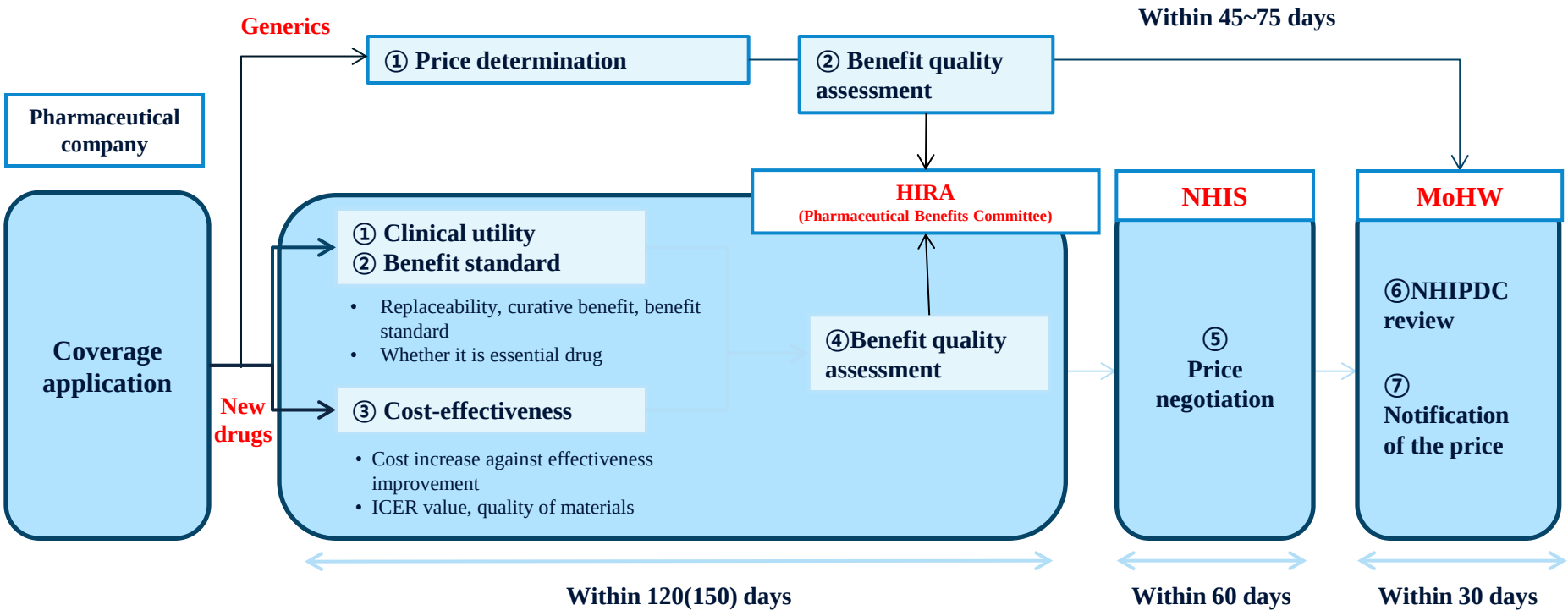
Current Status of NHI Expenditure on Pharmaceuticals



*** 162,098 (100 million KRW) = 14.5 Billion USD**

* Until 2013, figures for the 4 categories were adjusted to reflect fixed-cost fee schedules on top of the fee-for-service fee schedule. Since 2014, however, the 4 categories have been calculated based on fee-for-service fee schedule and therefore, the fixed cost charged by long-term care hospitals or for DRG are excluded from pharmaceutical expenditure.

Flow Chart of Coverage Decision for Drugs



1. Benefit assessment	- Pharmaceutical Benefits Committee	Coverage decision
2. Economic evaluation	- Economic evaluation Sub-committee	Economic evaluation, validity of submitted materials - Effectiveness and cost, appropriateness of model, etc.
3. Benefit standard review - New drugs - Anti cancer drugs	- Benefit standard advisory committee - Cancer deliberation committee	-Benefit standard setting considering clinical utility
4. Risk Sharing Review	- Subcommittee of risk sharing system	- Application of Risk Sharing Agreement, review validity of the proposed type

Pharmaceutical Benefits Committee

○ Composition: no more than 100 members (a pool of members), no more than 19 members (form a meeting)

○ Legal characteristics: **a consultative deliberation body of the president of HIRA** for **efficient assessment of the quality of pharmaceutical benefits**, etc.

○ Matters evaluated/assessed by the committee: **coverage of a new drugs, benefit criteria for new drugs, calculation criteria, ceiling prices for drugs**, etc.

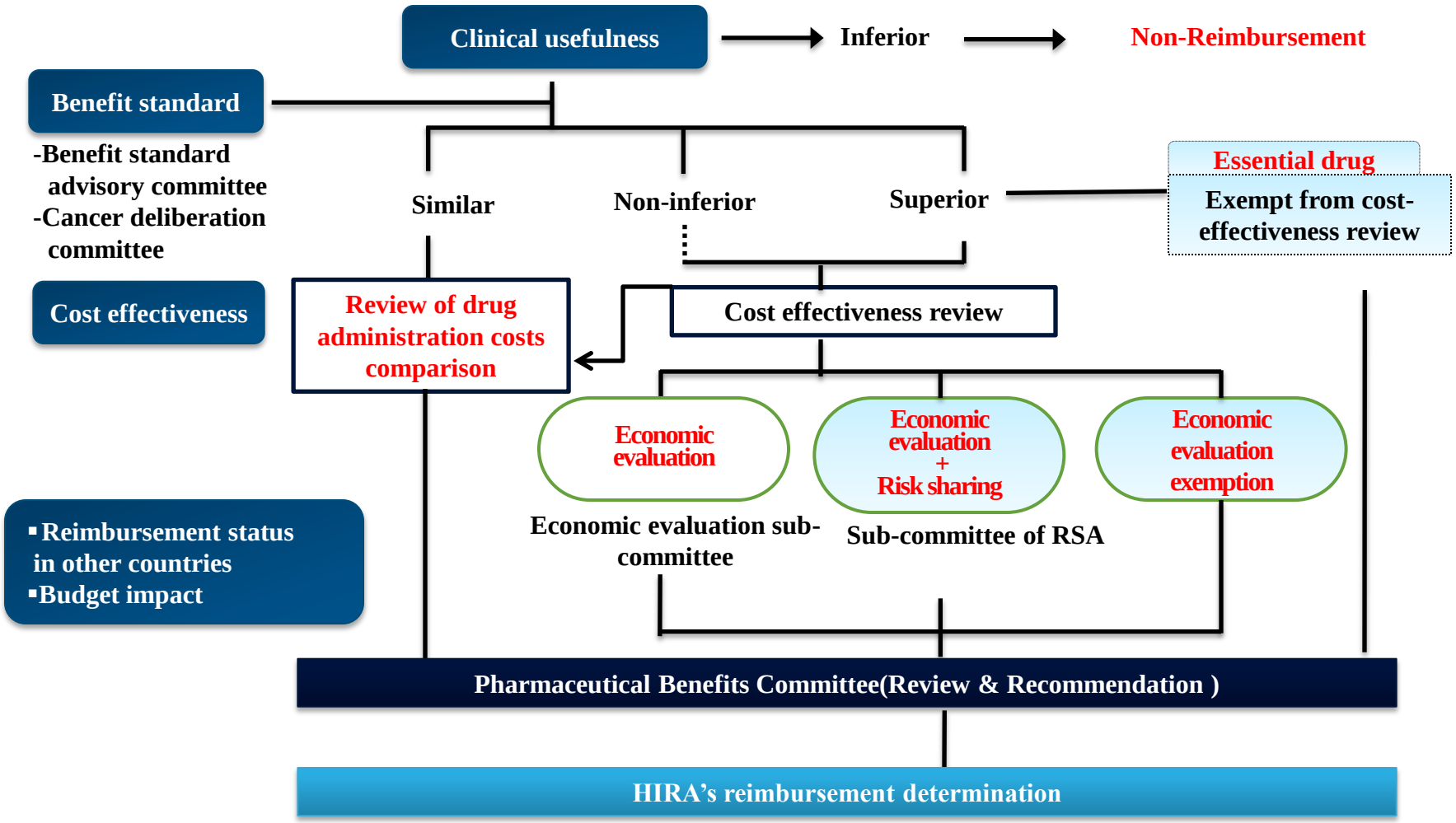
○ Subcommittees in place in the following areas: economic evaluation, risk-sharing agreements, pharmaceutical benefit criteria, financial impact assessment

Price negotiation by NHIS

○ Takes the following into consideration: assessment results of the Pharmaceutical Benefits Committee, expected volume of use, etc.

○ If negotiations fail, the Pharmaceutical Benefits Adjustment Committee makes adjustments for the "essential drugs for treatment."

Flow Chart of the New Drug Evaluation



*If the clinical usefulness is non-inferior, only cost-minimization analysis is possible

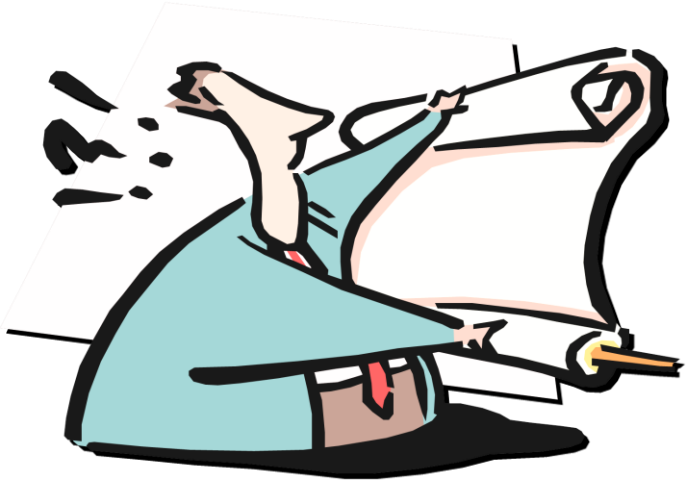
Selection Criteria for Reimbursement Approval

- A drug is clinically useful and cost-effective and has been evaluated as acceptable to reimbursement when considering reimbursement status and reimbursement prices in foreign countries, principles of reimbursement, insurance financing status
  - **Clinical usefulness** (fungible, severity of disease, therapeutic benefits)
  - **Cost-effectiveness** (drug administration cost, degree of improvement in clinical effects and cost-effectiveness)
  - **Impact on health insurance finance**(number of applicable patients, anticipated use volume, substitution effects with existing drugs or treatments)
  - **Reimbursement status in foreign countries**, reimbursement price

Number of New Drugs Evaluated per Year

- Number of New Drugs Evaluated per Year

2013	2014	2015	2016	2017	2018
61	48	81	65	83	58



03 Benefit Listing Procedure and Evaluation Criteria by Type of New Drug

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Benefit Listing Procedure and Evaluation Criteria by Type of New Drug

☞ **Essential Drug To Patient Care**

Economic Evaluation

Risk Sharing Agreement

Economic Evaluation Exemption Procedure

Administration Cost Comparison

Essential Drug To Patient Care

- **A drug meeting with all of the following subparagraphs**
  - A drug wherein no other substitutable treatments(including drugs) are available
  - A drug used for serious, life-threatening diseases
  - A drug proven for its clinically meaningful improvement, such as, significant extension of survival period of time

- **Price level of essential drug to patient care**
  - **The average level of adjust prices of A7** foreign countries

    (A7 = USA, Japan, UK, France, Germany, Swiss, Italy)

Essential Drug To Patient Care List

No.	Name of drug product	Indication
1	**Sprycel tab.**	1. Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML), with resistance or intolerance to prior therapy including imatinib. 2. Ph+ acute lymphoblastic leukemia(ALL) with resistance or intolerance to prior therapy.
2	**Cystadane pow.**	Homocystinuria.
3	**Naglazyme inj.**	Mucopolysaccharidosis VI(MPS VI; Maroteaux-Lamy syndrome).
4	**Elaprase inj.**	Hunter syndrome (Mucopolysaccharidosis II, MPS II).
5	**Myozyme inj.**	Pompe disease.
6	**Zavesca cap.**	Gaucher disease.
7	**Inovelon film-coated tab.**	Seizures associated with Lennox-Gastaut syndrome
8	**Remodulin inj.**	Pulmonary arterial hypertension
9	**Soliris inj.**	Paroxysmal nocturnal hemoglobinuria(PNH), treatment to reduce hemolysis)
10	**Carbaglu tab.**	Hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS)

Benefit Listing Procedure and Evaluation Criteria by Type of New Drug

Essential Drug To Patient Care

☞ **Economic Evaluation**

Risk Sharing Agreement

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Economic Evaluation

Cost-Effectiveness Evaluation

Cost effectiveness indicator and standard for decision-making

- **Economic evaluation** required : better effectiveness but, higher price proposed compared to reimbursed alternative
- Indicator : ICER (Incremental Cost-effectiveness Ratio)
- ICER Threshold : Not explicit and Using flexible value depending on
  - disease severity,
  - burden of illness,
  - impact to quality of life,
  - innovation

? ICER (Incremental Cost / Incremental effectiveness)

$$ICER = \frac{C_N - C_O}{E_N - E_O} = \frac{\triangle C}{\triangle E}$$

(Eg.) cost / QALY : cost for 1 year of life-year gained with perfect health status

* QALY : Quality adjusted life year
: standard unit for mix of quality and quantity of health benefit

The higher ICER value, the more opportunity cost occurred
The higher ICER threshold, the higher willingness to pay in the society

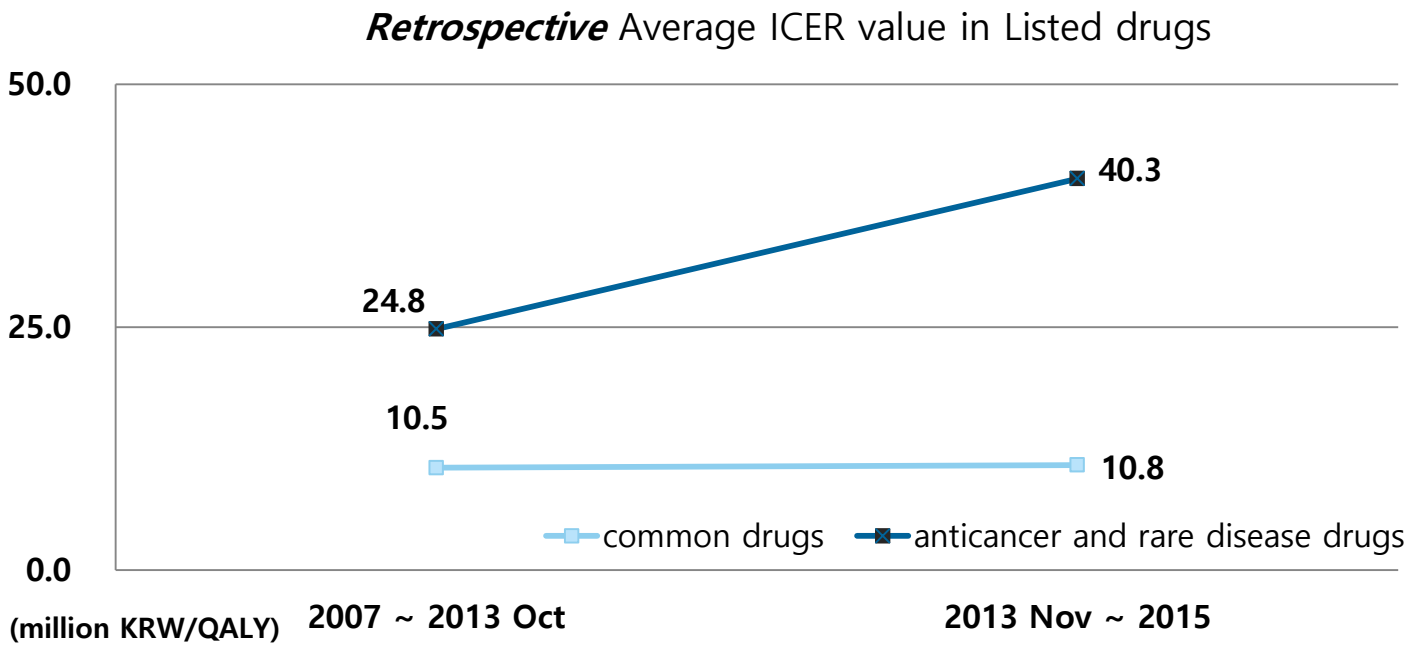
Economic Evaluation Enhancement of Access

Equitable Access to Medicine for severe disease (cancer & rare disease)

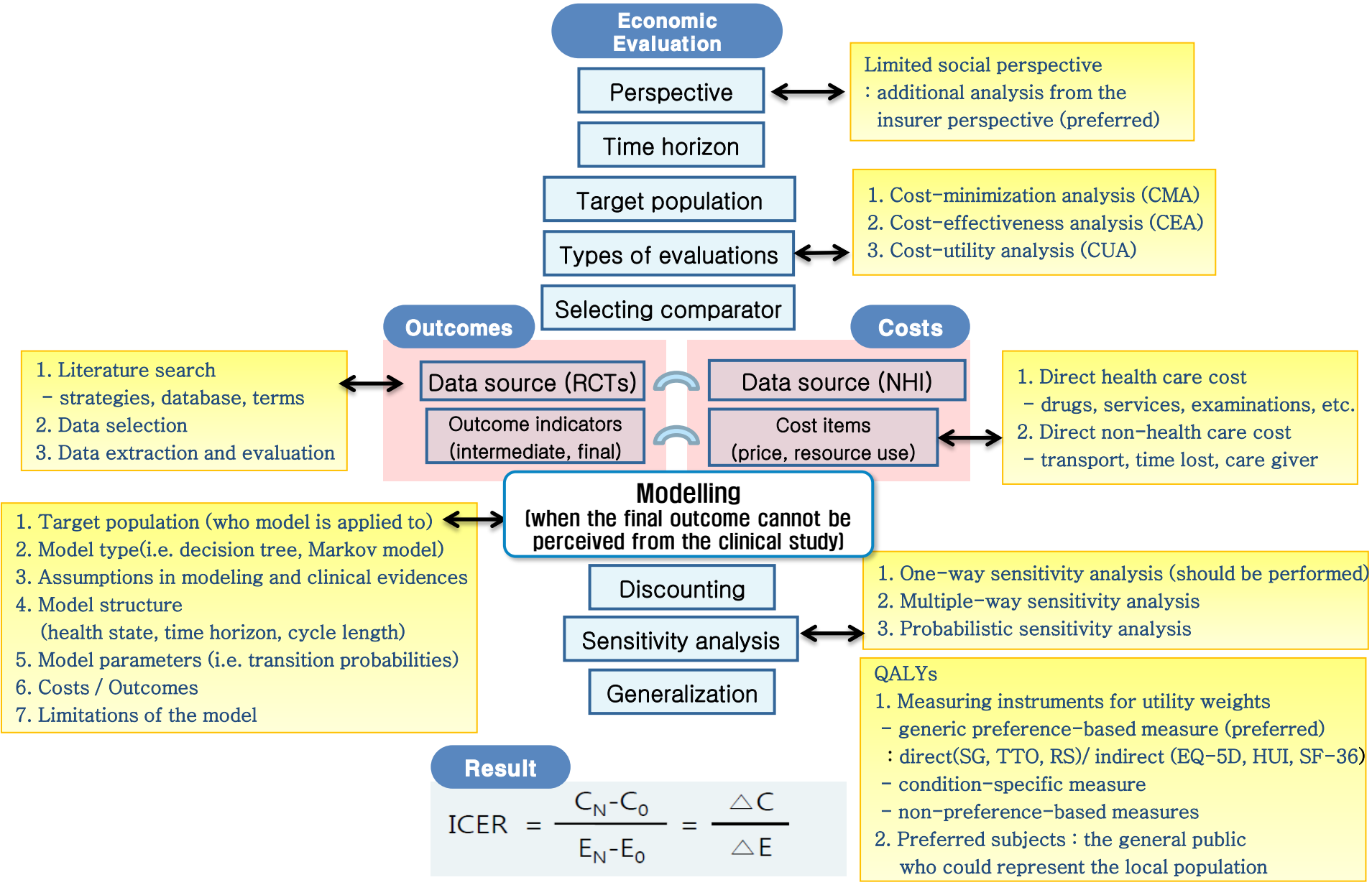
- **Flexible in considering threshold of ICER**

  National Task Force on Expanding coverage of Severe Diseases (2013.10)

  → increasing acceptable level of ICER for
  no alternative & life-threatening anti-cancer, rare disease treatments



Economic Evaluation Flow Chart



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Essential Drug To Patient Care

Economic Evaluation

☞ **Risk Sharing Agreement (RSA)**

Economic Evaluation Exemption Procedure

Administration Cost Comparison

Risk Sharing Agreement

- **Definition:** A contract between the insurer and pharmaceutical companies to share the risk of efficacy/effectiveness of a new drug and budget impact with pharmaceutical companies **(Jan. 2014 ~)**

- **Intent:** To secure the availability of irreplaceable and expensive drugs (such as anti-cancer medicine) while keeping the principle of selecting cost-effective drugs

- **Target:** Anti-cancer medicines that has no alternative or bioequivalence drug or treatment, orphan drugs that are used for life threatening condition

- **(Contract period)** Conventionally 4 years (3 years+1 year for evaluation)

Risk Sharing Agreement

Types of Risk Sharing Agreement

① **Continued treatment on condition + refund** (Continued administration depending on response and refund)

- After certain period of administration, evaluate each patient's response. Patients with positive response higher than the expectation will keep receiving the NHI benefit, and the reimbursement for the rest will be refunded to NHI by the applicant.

② **Cap on total amount** (Portion of benefit claim above certain amount is refunded)

- When annual drug benefit claim exceeds pre-set annual expenditure, portion of the excess is refunded by the applicant to the NHIS

③ **Refund** (Portion of claimed benefit is refunded)

- Portion of total drug benefit claim is refunded by the applicant to the NHIS

④ **Cap on each patient** (Portion of excess of each patient is refunded)

- Cap for each patient is pre-determined. When exceeded, portion of the excess is refunded by the applicant to the NHIS

Current Status of Drugs Included in RSA

No.	Ingredient	Classification	Indication	Type
1	**cetuximab**	Anticancer	colon and rectal cancer	Refund
2	**Enzalutamide**	Anticancer	metastatic castration-resistant prostate cancer	Refund
3	**crizotinib**	Anticancer	ALK-positive advanced non-small cell lung cancer	Refund
4	**eculizumab**	Rare disease	Paroxysmal nocturnal haemoglobinuria (PNH)	Refund
5	**Galsulfase**	Rare disease	Mucopolysaccharidosis VI	Refund
6	**regorafenib hydrate**	Anticancer	unresectable or metastatic gastrointestinal stromal tumours (GIST)	Refund
7	**pomalidomide**	Anticancer	relapsed and refractory multiple myeloma	Refund
8	**Pertuzumab**	Anticancer	HER-2 positive metastatic breast cancer	Etc.
9	**trastuzumab emtansine**	Anticancer	HER-2 positive metastatic breast cancer	Utilization Cap
10	**Pembrolizumab**	Anticancer	non-small cell lung cancer	Refund
11	**Nivolumab**	Anticancer	non-small cell lung cancer	Refund
12	**Palbociclib**	Anticancer	metastatic breast cancer	Refund
13	**osimertinib mesylate**	Anticancer	non-small cell lung cancer	Etc.
14	**Carfilzomib**	Anticancer	multiple myeloma	Refund
15	**Ramucirumab**	Anticancer	Gastric cancer	Refund
16	**Carbozantinib**	Anticancer	Lung cancer	Utilization Cap

Benefit Listing Procedure and Evaluation Criteria by Type of New Drug

Essential Drug To Patient Care

Economic Evaluation

Risk Sharing Agreement

☞ **Economic Evaluation Exemption Procedure**

Administration Cost Comparison

Economic Evaluation Exemption Procedure

Economic evaluation exemption procedure (May 2015)

Application criteria

Criteria	Contents
① Treatment agent for **rare disease or anti-cancer agent**	
② **Clinical need**	No alternative treatment methods (incl. drugs)
	No products or treatment methods that are in equivalent therapeutic positions that are used to treat serious, life-threatening disease
③ **The difficulty of producing evidence**	Approved by MFDS based on the data from a single-arm clinical trial without a control group
	Approved by MFDS based on the data from phase 2 clinical trial with a control group, without the phase 3 condition
	The difficulty of producing evidence is deemed difficult by the Committee due to the small number of target patients
④ A drug listed **in 3 or more of advanced 7 foreign countries** based on which the adjusted average foreign price is calculated as determined by the Committee	

*** Price of economic evaluation exemption**
- **the lowest price** of the adjust prices of A7 foreign countries

Economic evaluation exemption procedure List

No.	Drug product	Indication
1	**Caprelsa tab.**	Medullary thyroid cancer
2	**Adcetris inj.**	Hodgkin Lymphoma/Anaplastic Large Cell Lymphoma(HL/ALCL)
3	**Vimizim inj.**	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).
4	**Imbruvica cap.**	Mantle cell lymphoma(MCL)
5	**Zykadia cap.**	Crizotinib failed, ALK-positive, non-small cell lung cancer(NSCLC).
6	**Blincyto inj.**	Acute lymphoblastic leukemia(ALL)
7	**Diterin tab. (Generic of Kuvan tab.)**	Tetrahydrobiopterin(BH4)-responsive Phenylketonuria (PKU).
8	**Difitelio inj.**	Severe hepatic veno-occlusive disease (VOD), following hematopoietic stem-cell transplantation (HSCT).
9	**Zelboraf tab.**	Unresectable or metastatic melanoma with BRAF V600E mutation.
10	**Lynparza cap.**	BRCA-mutated advanced ovarian cancer
11	**Meqsel tab. (Mekinist tab.)**	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
12	**Olita tab.**	Locally advanced or metastatic EGFR T790M mutation-positive NSCLC (non-small cell lung cancer).
13	**Sylvant inj.**	Multicentric Castleman's disease (MCD), HIV(-) and HHV-8(-).
14	**Lartruvo inj.**	Soft tissue sarcoma
15	**Iclusig tab.**	Chronic myeloid leukemia(CML)
16	**Vyndaqel cap.**	Polyneuropathy
17	**Praxbind inj.**	Unique Reverse agent to dabigatran

Benefit Listing Procedure and Evaluation Criteria by Type of New Drug

Essential Drug To Patient Care

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☞ **Administration Cost Comparison**

Administration Cost Comparison

- **If the new drug's clinical utility is** "non-inferior or similar" **to alternative drugs,** the price of the new drug is **set as the "weighted average price of alternatives."**

  – Every year, there are not many new drugs applications that show superior clinical utility compared to alternative drugs. Accordingly, many new drug prices are set as the **"weighted average price of alternatives."**

Administration Cost Comparison

Omission of the drug price negotiation

- **For a drug whose price is evaluated to be set as the "weighted average price of alternatives,"**
  - If the pharmaceutical company accepts 90% - 100% of "weighted average price of replaceable drug" (considering the characteristics of new drugs such as the level of difficulty in development), the NHIS can skip price negotiation (60 days)

Type	Threshold price for negotiation exemption
① New ingredient, ② Biologics, ③ Orphan drug	Weighted average price of replaceable drug
④ Existing ingredient drug	Weighted average price * 0.9
⑤ pediatric drug	Weighted average price * 0.95

Thank you

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