厚生労働省 ひと、くらし、みらいのために Ministry of Health, Labour and Welfare

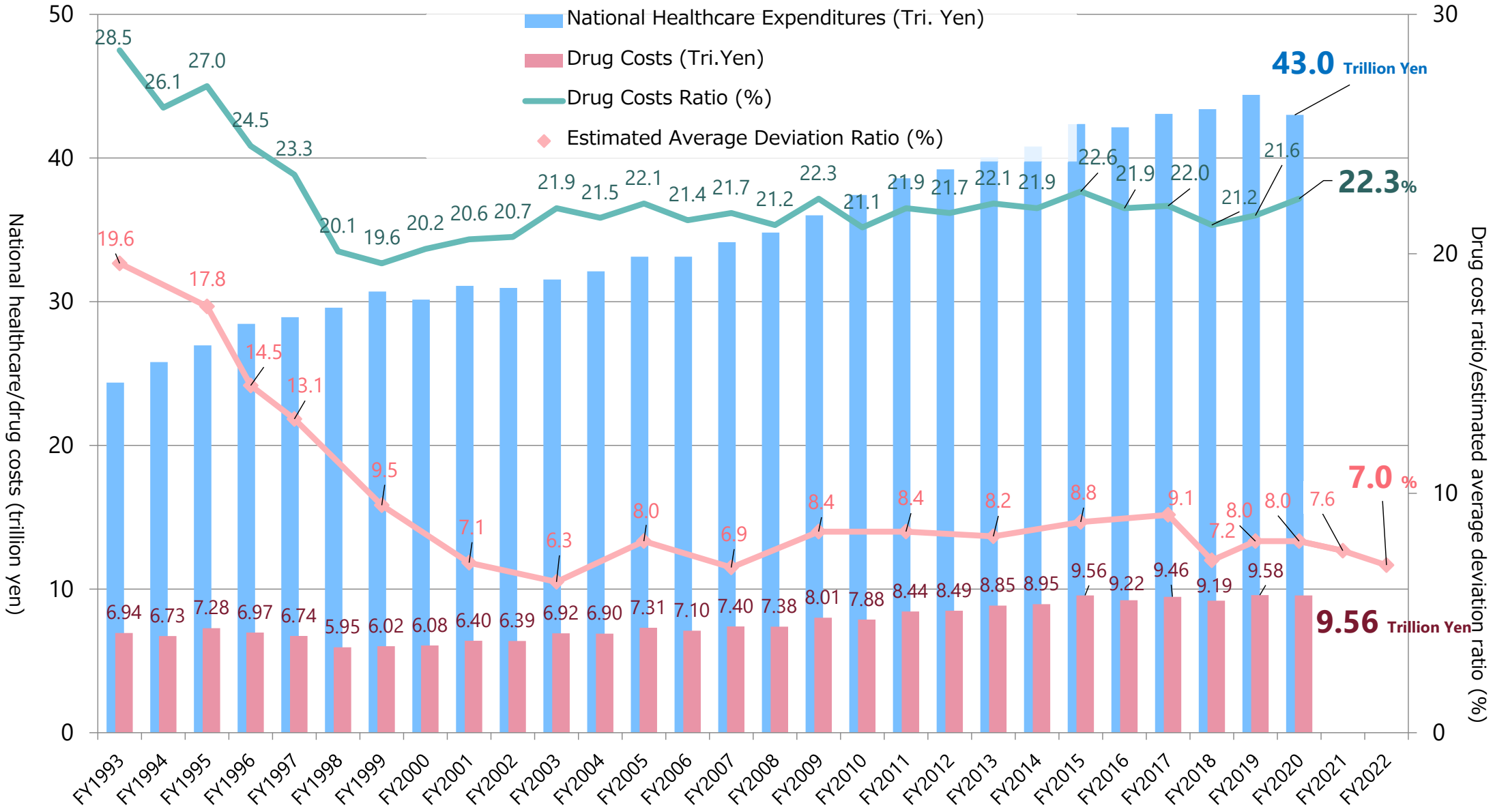
Japan's NHI Drug Price System

5th, 2023 11th Joint Conference of Taiwan and Japan on Medical Products Regulation

Policy Planning division for Pharmaceutical Industry Promotion and Medical Information Management,
Health Policy Bureau, MHLW

Ministry of Health, Labour and Welfare of Japan

Changes in National Healthcare Expenditures (NHE), Drug Costs, etc.



*The average deviation rate obtained in the drug price survey is regarded as the estimated deviation rate for the fiscal year.
*Estimated deviation rate in FY 2019 was deviation from the NHI price in April 2018
*Drug costs do not include those where drug costs such as DPC are calculated by including them in hospitalization fees

Analysis of the Impact of Drug Price Revision, etc. on the Pharmaceutical Market (Drug Costs)

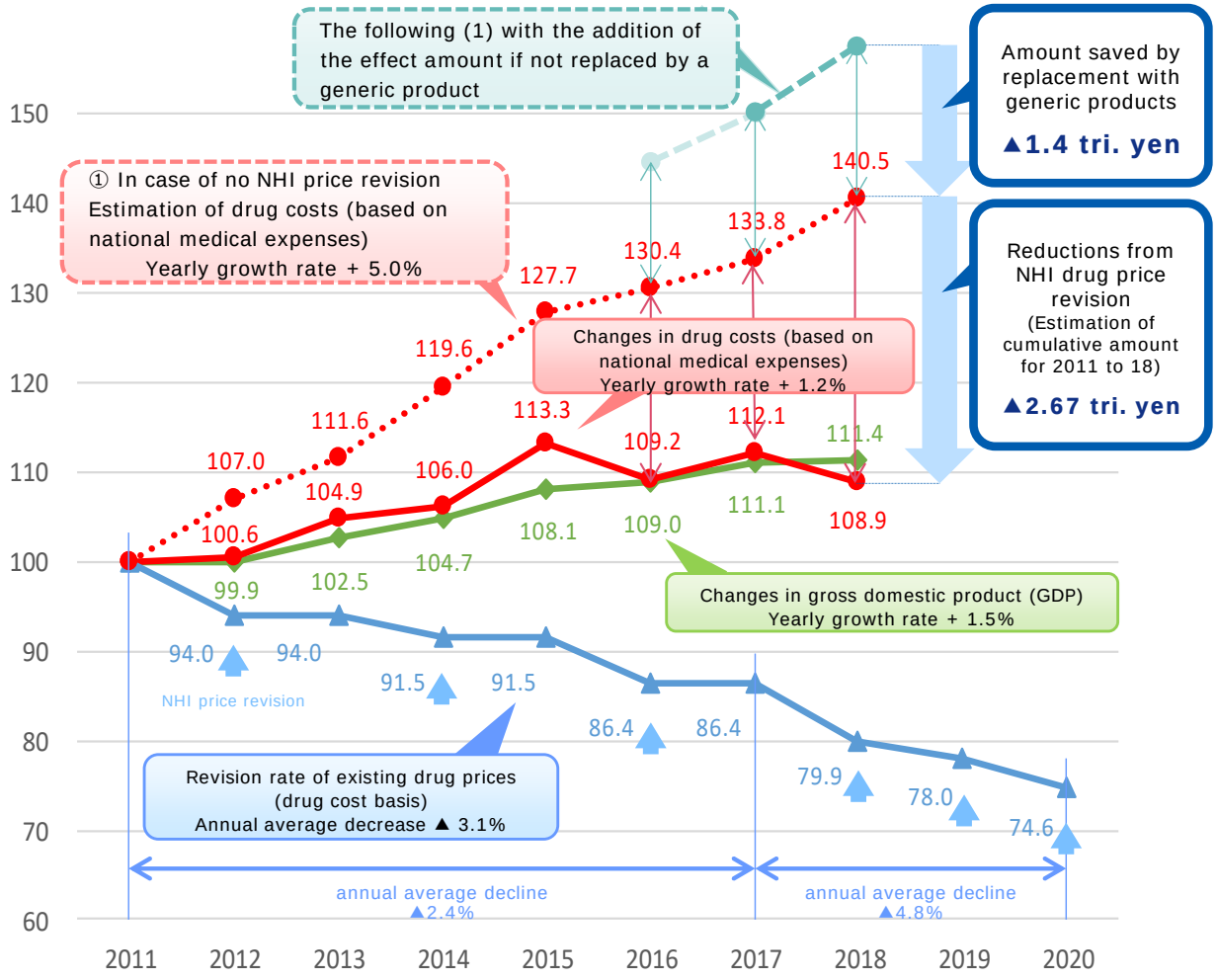
○ The growth rate of the drug market (drug costs) by 2018 was expected to increase by an annual average of 5.0% under the situation if the drug prices were not revised, but the biennial drug price revision suppressed the annual average increase to 1.2%.

*Due to the annual NHI drug price revision since 2018, the annual average reduction rate doubled from ▲ 2.4% (2011–17) to ▲ 4.8% (2017–20)

○ In addition, the growth of drug costs has been further suppressed by optimization of long-listed products and promotion of the use of generic products.

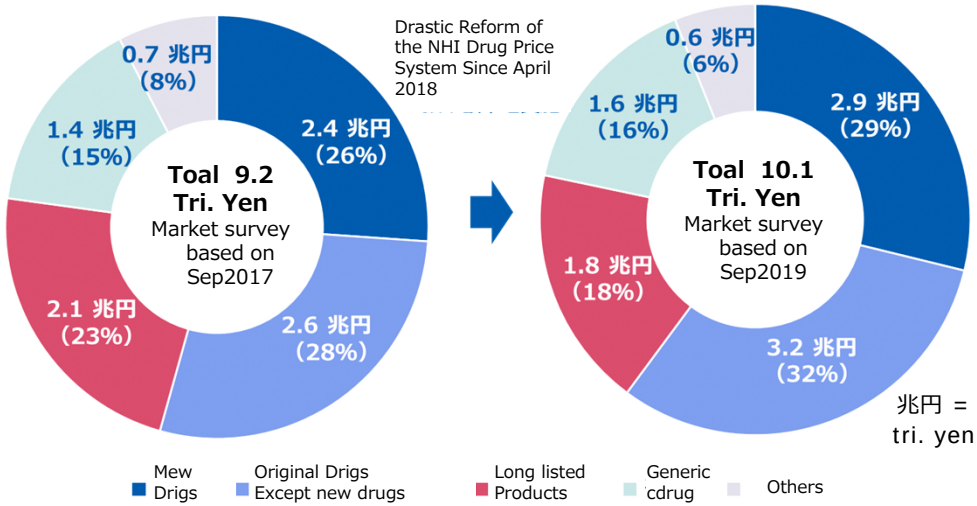
1. Changes in drug costs (%) compared to 1.2011 (23)

*For the drug cost/revision rate, the figure from "Chuikyo Drug-2 (3.8.4) " was used. For GDP, the figure from" Annual Estimate of National Accounts " by the Cabinet Office was used.



2. Changes in the composition ratio of drug costs

* The stated amount is the figure obtained by multiplying the transaction volume obtained in the drug price survey (for 1 month in the survey month) by the drug price and then multiplying it by 12 times (simple conversion to the annual figure)



3. Amount of proper effects of medical expenses by replacement with generic products

Drug price survey Fiscal year¥	Generic Usage rate	Drug costs of the original product if it is not replaced with a generic product Difference from the drug costs of generic drugs
FY2017	65.8%	1.3 trillion yen
FY2018	72.6%	1.4 trillion yen ※1. Used for trial calculations
FY 2019	76.7%	1.62 trillion yen
FY 2020	78.3%	1.86 trillion yen

Overview of Medical Service Regime in Japan

- 75 years or older
  10% copayment
  (Those with income comparable to current workforce have a copayment of 30%.
  Except for those whose income is comparable to the current workforce; those persons whose income is a certain level or higher must bear 20% of the medical costs (copayment) effective from October 1, 2022.)
- 70 to 74 years old
  20% copayment*
  (Those with income comparable to current workforce have a copayment of 30%)
- Start of compulsory education to 69 years old
  30% copayment
- Yet to start compulsory education
  20% copayment

Patient (insured)

Copayment: 5 trillion yen

(2) Receive service & copayment

(3) Clinical service

Medical expenditure: ¥43 trillion

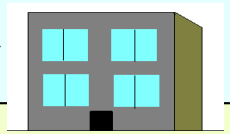
Insurance premium: ¥21.3 trillion

(1) Insurance contribution

(5) Payment

(4) Claims

Insurer



[Medical insurance system]

Administrative bodies

National

Prefectural

Municipal governments

Public funding

Public funding

Supportive contribution

Respective insurer

(Principle schemes)	(Number of insurers)	(Number of enrollment)
National Health Insurance	1,716	approx. 26 million
Japan Health Insurance Association administered health insurance	1	approx. 40 million
Association/union administered health insurance	1,388	approx. 29 million
Mutual aid association	85	approx. 9 million

* No. of insurers and enrollments as of March 31, 2021

Medical Care System for the Elderly Aged 75 and Over	47	approx. 18 million

* Number of those enrolled is as of the end of March 2021

[Medical Service Regime]

Hospital:	8,205
(Number of beds:	1,500,057)
Clinic:	104,292
(Number of beds:	83,668)
Dental clinic:	67,899
Pharmacy:	60,171

* Numbers as of October 1, 2021
(Source: 2021 Survey of Medical Care Institutions)

* No. of pharmacies as of March 31, 2019
(Source: FY2019 Report on Public Health Administration and Services)

Physician	339,623
Dentist	107,443
Pharmacist	321,982
Registered nurse	1.32 million
Public health nurse	67,000
Midwife	42,000

* No. of physicians, dentists, and pharmacists as of December 31, 2020
(2020 Survey of Physicians, Dentists and Pharmacists)

* No. of registered nurses, public health nurses and midwifes as of 2020
Statistics of the Nursing Division, the MHLW

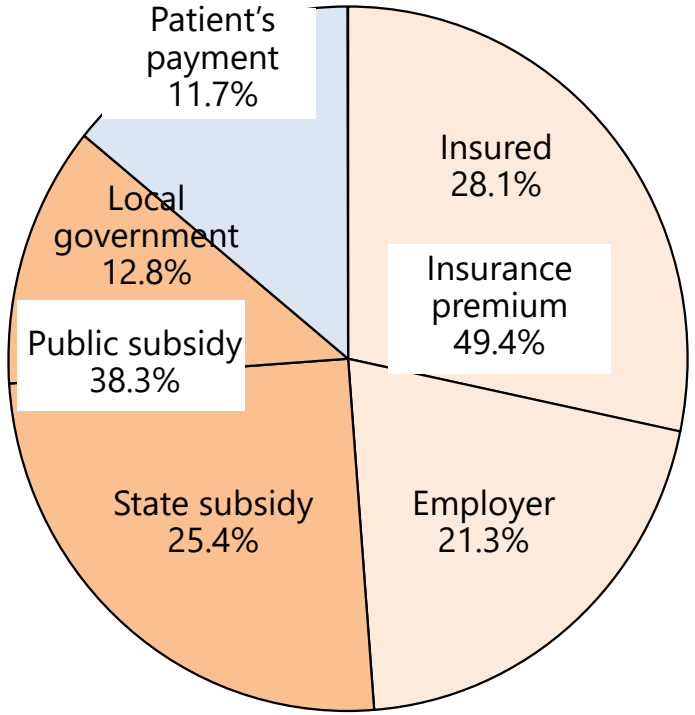
Meaning of the Universal Health Insurance System

- ○ Our country has realized the world's highest level of life expectancy and healthcare standards through the universal health insurance system.
- ○ It is necessary to continuously ensure safe and secure lives of the citizens by firmly maintaining the universal health insurance with the current social insurance system.

[Characteristics of Japanese universal health insurance system]

1. Covering all citizens through public medical insurance
2. Freedom of choice of medical institution (free access)
3. High-quality medical services with low costs
4. Based on the social insurance system, spending the public subsidy to maintain the universal health insurance

Proportion of the burden of national medical expenses in Japan (by resource) (FY2019)



Overview of the Current NHI drug price system

1. The drug price standard sets the price of drugs when they are paid by the medical insurance to health insurance medical institutions or health insurance pharmacies (health insurance medical institutions, etc.).

2. The NHI drug price standard was announced by the Minister of Health, Labour and Welfare based on the "Standards for Drug Pricing" prepared by the Chuikyo on February 7, 1990.

3. The prices specified in the NHI drug price standard shall be periodically revised based on the results of investigation (drug price survey) of the actual sales price (market price) to medical institutions and pharmacies.

National Health Insurance Drug Price Standard

Items and prices of drugs usable in insurance-covered healthcare, specified by the Minister of Health, Labour and Welfare
(common for all medical insurance systems, including health insurance, National Health Insurance (NHI), and various mutual aid systems)

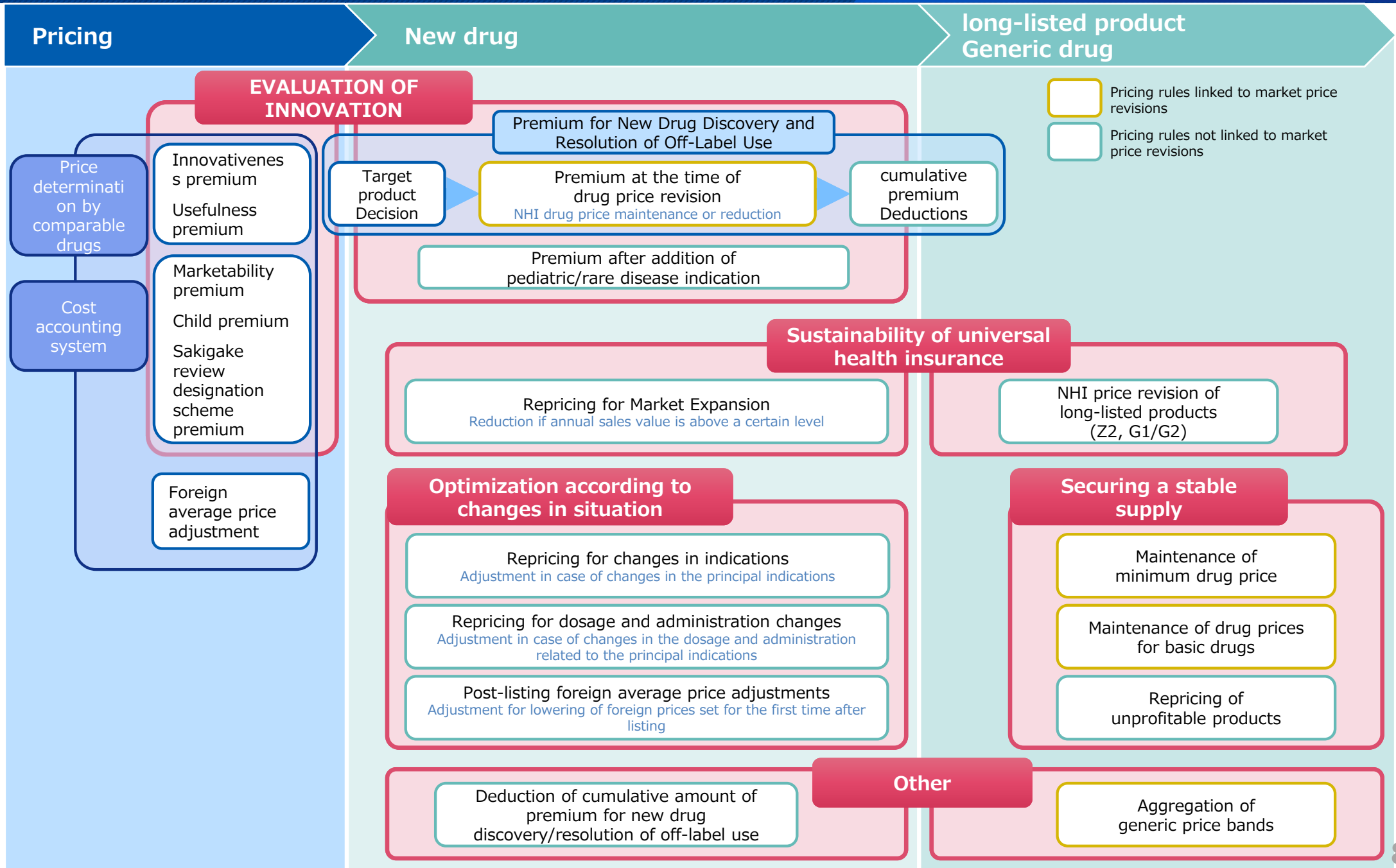
- Item list
  - A doctor or pharmacist operating under the health insurance program, in principle, must not use drugs other than “Drugs the Minister of Health, Labour and Welfare specifies”.
  - Items listed in the NHI Drug Price Standard are stipulated as “Drugs the Minister of Health, Labour and Welfare specifies”.

  = NHI Drug Price Standard specifies drugs usable in insurance-covered healthcare, and functions as an item list.

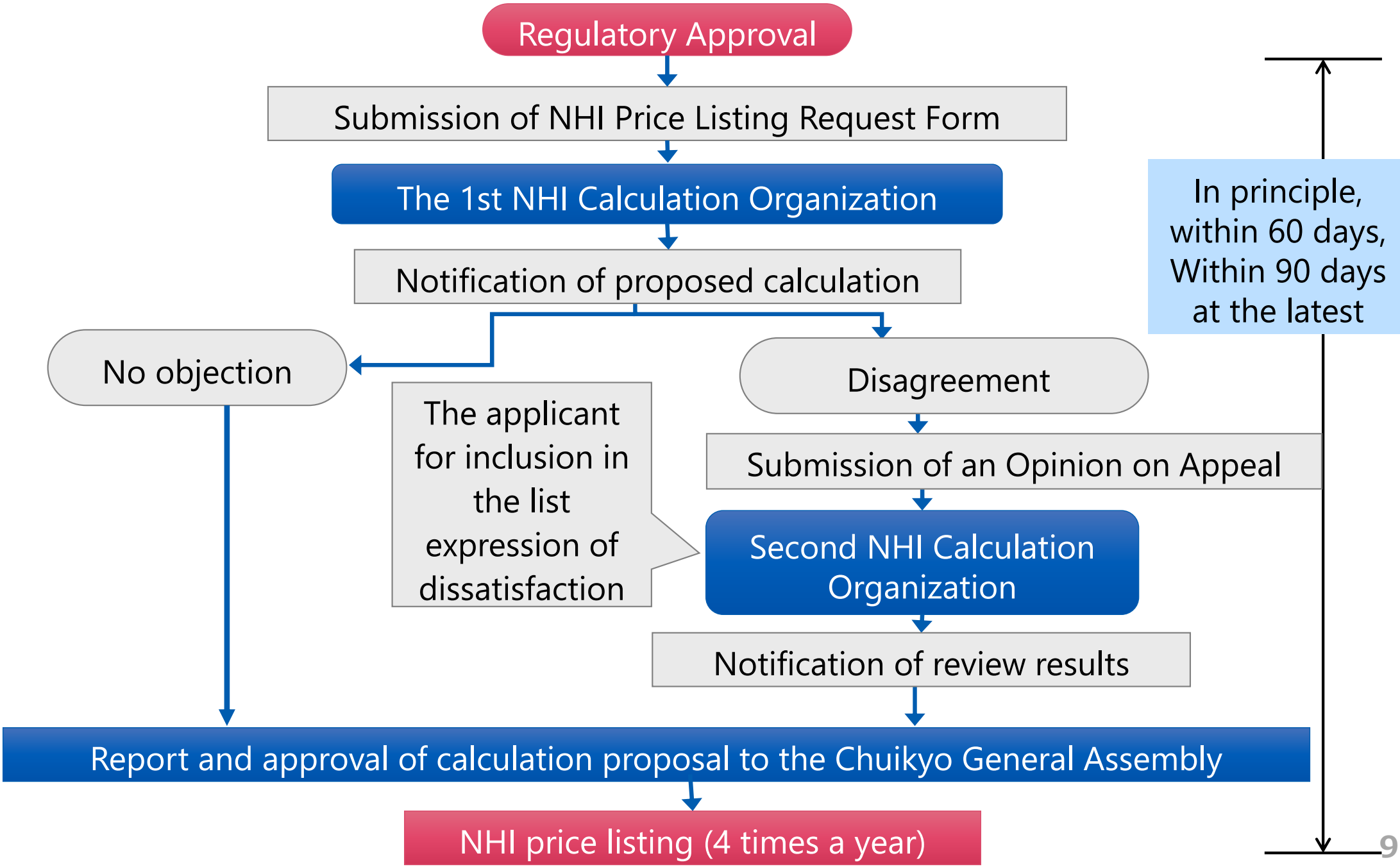
- Price table
  - When an authorized medical institution or pharmacy operating under the health insurance program makes insurance claims, the drug charge shall be calculated based on the price specified in the NHI Drug Price Standard.

  = NHI Drug Price Standard specifies the claimable amount of drugs used in insurance-covered healthcare, and functions as a price table.

Life Cycle of Drugs and Current Drug Pricing Rules (Overall Image)



New Drug Price Calculation Method for New Drugs (Overall picture)



Drug Pricing Process

General Meeting (Chuikyo)
(established in 25)

Reports

Reports

Special Committee on Drug Prices *(established in 1990)*
- Investigation and deliberation of technical matters related to drug price system reform
- Preparation of drug pricing standards once every 2 years and reporting to the General Meeting

Reports

Drug Pricing Organization *(established in 2000)*
- Members are experts in medicine, dentistry, pharmacology, and health economics.
- In accordance with the drug pricing standards and Regarding individual products examine the following and report to the general meeting
  - Calculation of new drugs, (quarterly listing)
  - Examination of premium rates for repricing for market expansion, etc. (every 2 years)
  - Other (consideration of drug classification, etc.) (as needed)
- Opinions on revision of drug pricing system, compile, report to the Special Committee on Drug Prices, (every 2 years)

New Drug Price Calculation Method for New Drugs (Overall picture)

Basic Approach to Calculating NHI Drug Prices

Similar drugs: drugs that are similar in the following respects
(a) Indications and effects
(b) Pharmacological action
(c) Composition and chemical structural formula
(D) Dosage form, dosage category, dosage form and usage

New drugs

New drugs with little novelty
(Not subject to correction addition, more than 3 drugs with similar pharmacological actions exist)

Similar drugs available

Similar drug effect comparison method (I)

Match the daily drug price of new drugs to the daily drug price of existing similar drugs (most similar drugs)

compensating addition

Breakthrough Addition (70-120%)
Usefulness Addition (5-60%)
Marketability Addition (5-20%)
Children Addition (5-20%)
Specific use Addition(5-20%)
Pioneer Addition (10-20%)

Similar drug effect comparison method (II)

Lowest price compared to the daily drug price of similar drugs over the past several years

⇒ Either (1) or (2), whichever is lower.
(1) Average of similar drugs over the past 10 years
(2) Lowest price for similar drugs in the past 6 years

⇒If the amount exceeds the amount calculated by the Comparable Drugs Method (I), the lowest price including that amount and (iii) and (iv) below.
(iii) Average of similar drugs over the past 15 years
4) Lowest price of similar drugs in the past 10 years

No similar drugs

Cost accounting method

- Cost of manufacturing and imports
- General and administrative and selling expenses (50.4% or less)
- Operating income (16.1% or less)
- Distribution expenses (7.3% or less)
- Sales tax

Compensating addition
(Same as " Similar drug effect comparison method I")

Breakthrough Addition (70-120%)
Usefulness Addition (5-60%)
Marketability Addition (5-20%)
Children Addition (5-20%)
Specific use Addition (5-20%)
Pioneer Addition (10-20%)

Foreign Average Price Adjustment※

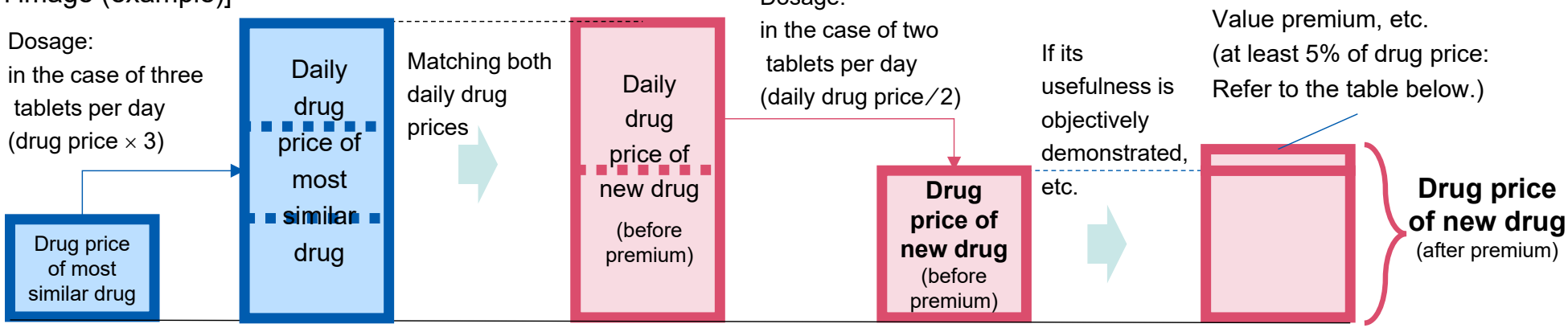
Similar Efficacy Comparative Method (I)

Calculation rule

- If there are similar drugs* to a new drug to be newly listed in the drug price standard, the daily drug price of the new drug shall be matched to that of the drug with the highest similarity (most similar drug) from the perspective of ensuring fair competition in the market.
- If it is objectively demonstrated that the new drug is more useful than the similar drug, a corrective premium shall be applied to the above amount.

*Similar drug: Those drugs having similarities in terms of (a) to (d); (a) indication and effect, (b) pharmacological action, (c) composition and chemical structural formula, and (d) administration route, dosage form category, and dosage form and dosing regimen

[Calculation image (example)]



Types of corrective premiums	Premium rate	Object
Innovation premium	70% to 120%	New action mechanism, high efficacy and safety, improvement in disease treatment methods
Value premium	5% to 60%	High efficacy and safety, improvement in disease treatment methods, etc.
Marketability premium	5%, 10% to 20%	Orphan drugs, etc.
Pediatrics premium	5% to 20%	Dosage explicitly including those relating to children, etc.
Specific use premium	5% to 20%	Newly listed products that are designated as a specific use drug
SAKIGAKE premium	10% to 20%	Newly designated as SAKIGAKE (SAKIGAKE designation system)

Similar Efficacy Comparative Method (II)

Calculation rule

For new drugs with little novelty (*),

1. In principle, the price shall be set at (1) or (2), whichever is lower.
   (1) Average daily drug price of similar drugs listed in the past 10 years
   (2) The lowest daily drug price of similar drugs listed in the past 6 years

*New drugs with little novelty:
New drugs outside the scope of corrective premiums, having at least three drugs with similar pharmacological actions (= “fourth” drug or later with no premiums)

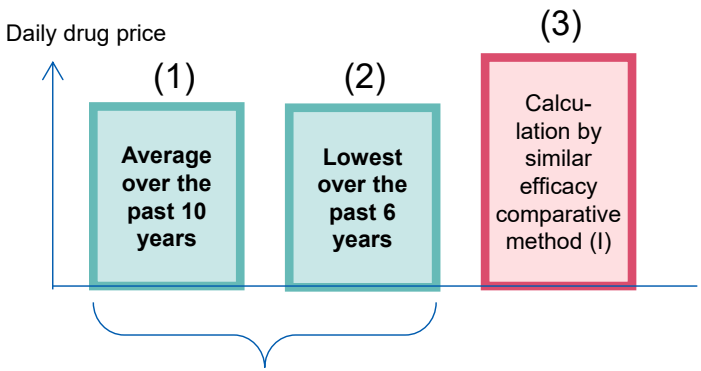
2. If the prices (1) and (2) are higher than “(3) amount calculated by the similar efficacy comparative method (I) (daily drug price of the most similar drug),” the following prices shall be calculated:
   (4) Average daily drug price of similar drugs listed in the past 15 years
   (5) The lowest daily drug price of similar drugs listed in the past 10 years

The amount shall be set at the lowest of (3) to (5).

Note: For pharmaceuticals outside the scope of the price maintenance premium that are calculated by the similar efficacy comparative method (II), an amount equivalent to cumulative addition of the price maintenance premium for a comparative drug (a total of an average price maintenance premium rate in each fiscal year when the price maintenance premium was applied) shall be deducted.

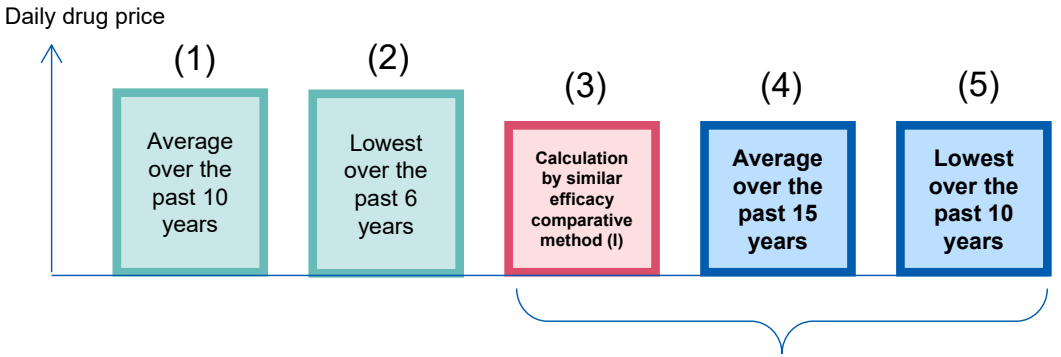
[Calculation image (example)]

In the case of (3) ≥ (1) and (2)



The price shall be matched to the daily drug price of (1) or (2), whichever is lower.

In the case of (1) and (2) > (3)



The price shall be matched to the daily drug price of (3), (4), or (5), whichever is the lowest.

Cost Calculation Method

- If there are no similar drugs, add up material costs, manufacturing expenses and other items.

(Example)

(1) Material costs	(Active ingredients, excipients, containers and boxes, etc.)
(2) Labor costs	(= 3,636[Note 1] × working hours)
(3) Manufacturing expenses	
(4) Product manufacturing (import) cost	
(5) Selling expenses, research expenses, etc.	((5)／((4) + (5) +(6)) ≤ 0.505[Note 2])
(6) Operating profit	((6)／((4) + (5) + (6)) = 0.166[Note 2])
(7) Distribution costs	((7)／((4) + (5) + (6) + (7)) = 0.071[Note 3])
(8) Consumption tax	(10%)
Total: Calculated drug price	

However, the upper limit of the selling, general, and administrative (SGA) ratio shall be 70% for chemical products with a degree of disclosure ≥ 80% and for biopharmaceuticals with a degree of disclosure ≥ 80% and in which only research and development expenses exceed the upper limit of the SGA ratio (50.6%) (limited to those with a peak market size of less than 5 billion yen).

For regenerative medicine products, the distribution cost shall be closely investigated for each item. If it is lower than the amount calculated by the average coefficient, the lower amount shall be used for calculation.

Note 1 Unit labor cost: “Monthly Labour Survey” and “General Survey on Working Conditions” (Ministry of Health, Labour and Welfare)
Note 2 Selling, general and administration expenses ratio operating profit margin: “Handbook of Industrial Financial Data” (Development Bank of Japan Inc.)
Note 3 Distribution cost ratio: “Statistics on Pharmaceutical Industry Report” (Economic Affairs Division, Health Policy Bureau, Ministry of Health, Labour and Welfare)
In principle, the above figures shall be the average coefficients in the pharmaceutical industry (averages over the last three years [2019 to 2021] obtained at the end of the previous fiscal year).

- If the new drug is found to be more useful than existing therapies, a corrective premium shall be applied to the above amount.
- However, the premium rate shall vary depending on the percentage of parts that can be disclosed by the drug pricing organization (degree of disclosure) out of the total product cost.

Amount of the premium = Total price (Price before premium) × Premium rate (0% to 120%) × Premium coefficient (0 to 1)

Degree of disclosure	80% or more	50% to 80%	Less than 50%
Premium coefficient	1.0	0.6	0

* Degree of disclosure = (Parts of the drug price that can be disclosed)／(Total product cost: (4), (5))

Foreign Average Price Adjustment

From the viewpoint of securing fair market competition, price adjustment shall be performed when there is a large discrepancy with the foreign price (1.25 times or more or 0.75 times or less of the foreign average price) in the cost calculation method or the similar efficacy comparison method for products without similar pharmacological actions.

Calculation Rules

1. Foreign average prices are the average of prices in the U.S. (Medicare/Medicaid), the U.K., Germany and France
   *If there are 2 or more foreign prices and the highest price is more than 2.5 times the lowest price, the average of the foreign prices excluding the highest price
   *If there are three or more foreign prices and the highest price is more than twice the average of the other prices, the average of the foreign prices calculated by regarding the highest price as twice the average of the other prices
2. Price adjustments are implemented in the following cases (adjusted to approximate the foreign average price)
   (1) For exceeding 1.25 times the foreign average price → **reduction** (Equation (1))
   (2) For **below 0.75 times** the foreign average price → **raise** or (Equation (2))

[Equation]

① > 1.25 fold

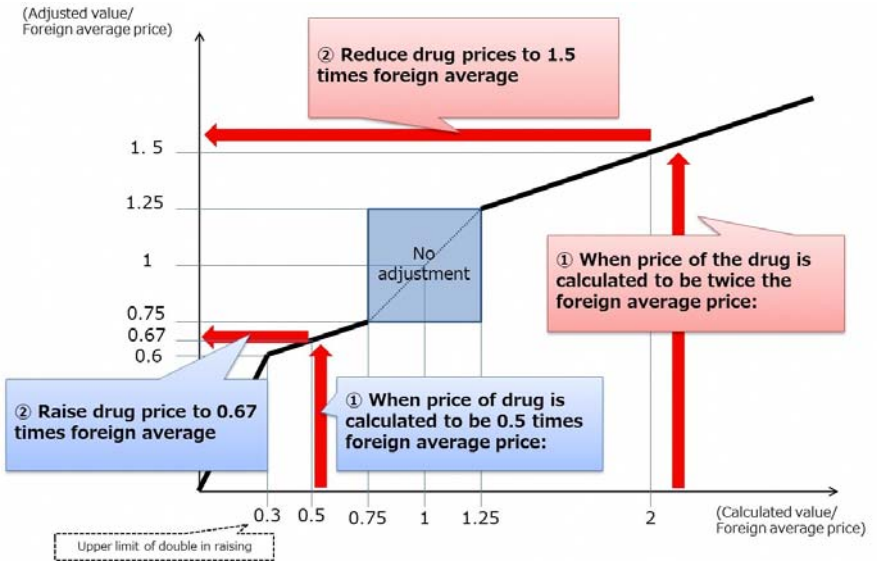
$$\left(\frac{1}{3} \times \frac{\text{Calculated value}}{\text{foreign average price}} + \frac{5}{6} \right) \times \text{foreign average price}$$

② Below 0.75 times

$$\left(\frac{1}{3} \times \frac{\text{Calculated value}}{\text{foreign average price}} + \frac{1}{2} \right) \times \text{foreign average price}$$

(Up to twice the calculated value)

Image of Foreign Average Price Adjustment



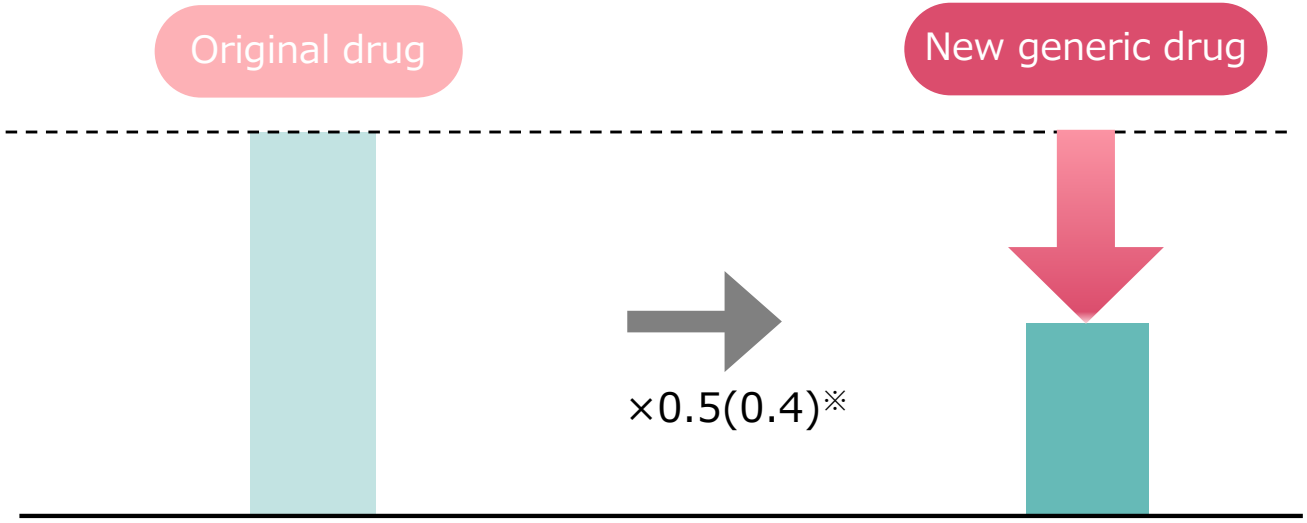
NHI Pricing Method for New Generic Drugs

When generic drugs are first listed

It shall be the price of the original drugs multiplied by 0.5.
For oral drugs, it shall be the price multiplied by 0.4 if the number of brands exceeds 10.
For biosimilar, it shall be the price of the original biological drugs multiplied by 0.7.

When generic drugs were already listed

It shall be the same price as the minimum price of generic drugs listed already (if any, the same price as the price of drug in the same company).

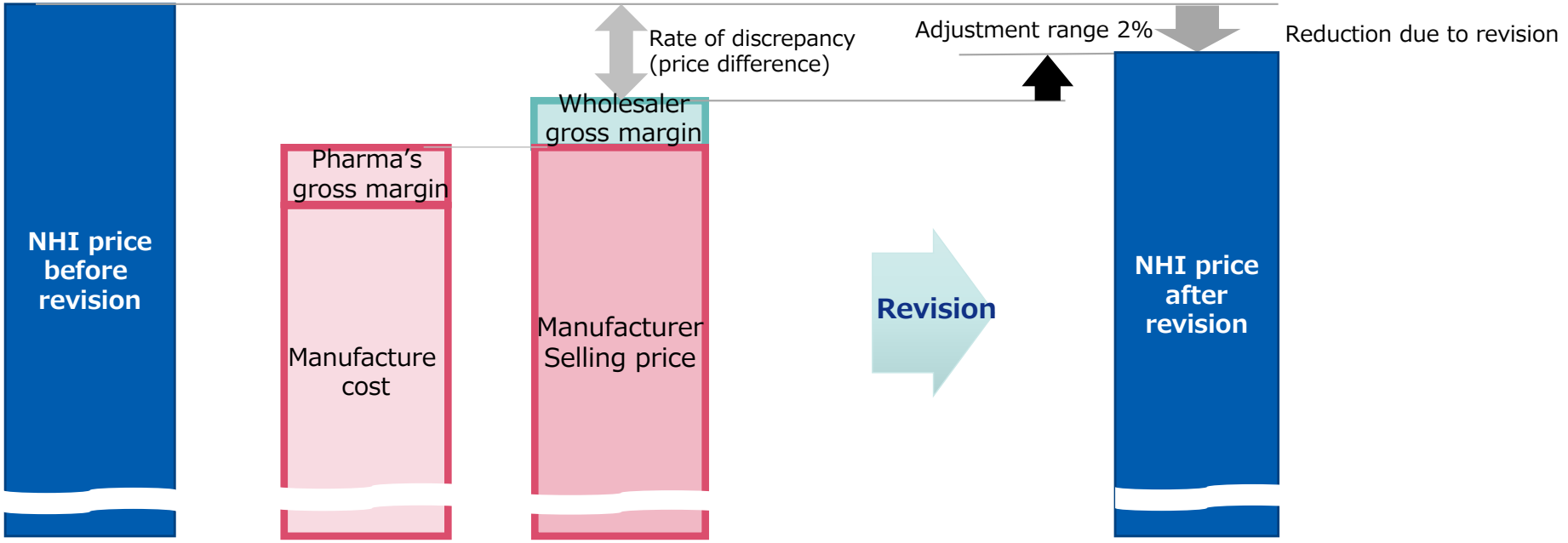


※ For oral drugs, 0.4 times if the number of brands exceeds 10.

Image of Drug Price Revision
(weighted average of market prices with adjustment margin method)

At the time of drug price revision, the price (drug price) of drugs shall be revised to the weighted average of the current market price (*) of each product with the addition of an adjustment margin (However, the price before revision is the upper limit)

* Actual market price: the actual transaction price from wholesalers to medical institutions/pharmacies (wholesaler price)



[Reference] Calculation method of weighted average of current market prices with adjustment margin method

New drug price = [The sales price to medical institutions/pharmacies Weighted mean (market price excluding tax)] × (1 + tax rate) + Adjustment range

*Including local consumption tax

Adjustment range: The amount equivalent to 2% of the pre-revision price as **adjustment range to stabilize drug distribution**

Premium for Promotion of New Drug Discovery and Resolution of Off-Label Use: Addition of Target Products, etc.

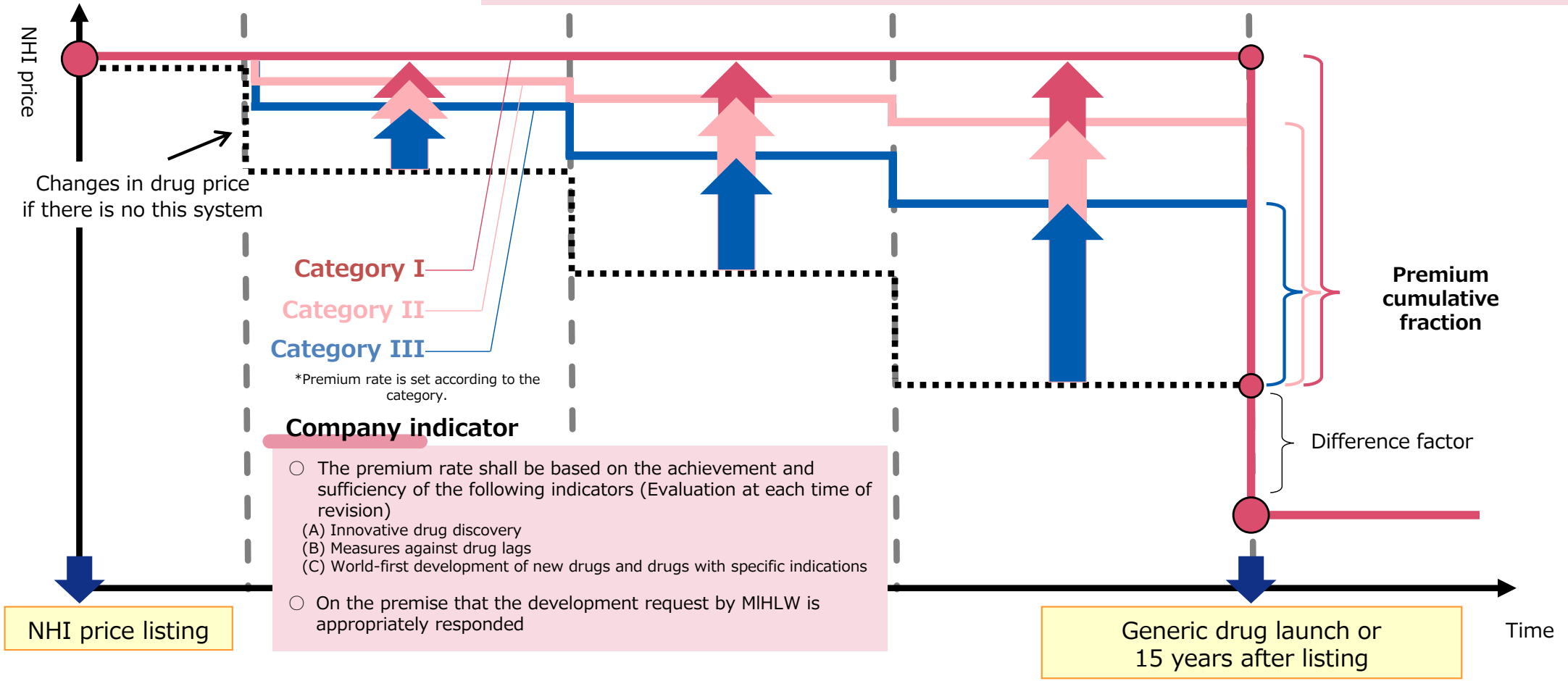
Positioning of the system

To efficiently and effectively promote the creation of innovative new drugs, a suspension of drug price reduction based on current market prices of new drugs without generics

item requirement

Judgement focusing on innovativeness and usefulness of the drug itself

① Drugs for which the innovation premium, utility premium, and operating profit margin adjustment have been applied (including drugs with additional indications equivalent to these premiums), ③ Products publicly offered for development, ③ Orphan drugs, ④Drugs with novel mechanisms of action (Only those that are found to be innovative and useful in reference to the standards.), ⑤ Drugs with novel mechanisms of action that are within 3 years or within the third rank from drugs with novel mechanisms of action are products eligible for the premium or products meeting the standards, ⑥ Pioneering drugs, ⑦ Drugs for specific use, and ⑨ Drugs for the treatment of drug-resistant bacteria



Company indicator

○ The premium rate shall be based on the achievement and sufficiency of the following indicators (Evaluation at each time of revision)
(A) Innovative drug discovery
(B) Measures against drug lags
(C) World-first development of new drugs and drugs with specific indications

○ On the premise that the development request by MlHLW is appropriately responded

*The premium amount will be capped according to the discrepancy rate.

Review of the Premium to Promote the Development of New Drugs (Requirements for Companies, etc.)

- ○ Add vaccines and therapeutic drugs newly approved for COVID-19 (in the past 5 years) to the company indicators for the PMP (4 points for one product)
- ○ position “pioneering drugs ” and“ drugs for specific use ” as corporate indicators
- ○ Category III was expanded (changed to 2 points or less) in consideration of the balance of the number of companies in relation to the premium coefficient for the PMP.

< Company indicators >

	Description of the indicator	
A-1	Domestic studies (including multi-regional clinical trials including Japan) (Number of studies conducted) (Phase II and subsequent studies)	Top 25% 4 pts Moderate 50% 2 pt
A-2	Number of listed ingredients * 1 (past 5 years)	Top 25% 4 pts Moderate 50% 2 pt
A-3	Enrollment performance of innovative new drugs (past 5 years)	2 pts with results
A-4	Past listing of drugs for the treatment of drug-resistant bacteria (past 5 years)	2 points for one product
A-5 Newly established	Drugs for the treatment of COVID-19, etc. (past 5 years)	4 points for one product
B-1	Products publicly offered for development (No. of development starts) (past 5 years) (excluding B2 minutes)	2 points for one product
B-2	Products publicly offered for development (number of approvals obtained) (past 5 years)	2 points for one product
C-1	World-first development of new drugs (number of products) (past 5 years)	2 points for one product
C-2 Newly established	Drug development for specific application (number of products) (past 5 years) (except for A-4 minutes)	2 points for one product

< Classification method >

Category	I	II	III
Range	Top 25% *	Other than I and III	Not more than 2 pt
addition coefficient	1.0	0.9	0.8

* Regarding A -5, it includes vaccines only if it is used for the treatment or prevention of the infection caused by the novel coronavirus and the therapeutic or preventive effect against the infection caused by the novel coronavirus has been clarified by the regulatory review.
* For C -1, the designated number of Pioneering Medicinal Product.
* Regarding C -2, it is the designated number of drugs for specific use.

Premium at the Time of Drug Price Revision

Calculation rules

1. Listed products for which additional indications and effects etc. for children have been added

- Additional indication or dosage and administration for pediatric patients

*However, public knowledge-based application and other applications for which the burden on the marketing authorization holder is considered to be fairly low shall be excluded (Same for the following 2 to 4)

2. Listed Products with Additional Indications and Effects for Rare Diseases

- Products with additional indications or dosage and administration for orphan diseases (only orphan drugs or drugs considered to be equivalent)

3. Listed products with additional pioneering indications, etc.

- Innovative products with additional indications or dosage and administration

4. Listed products with additional indications and effects etc. for specific uses

- Specified drug with additional indication or dosage and administration

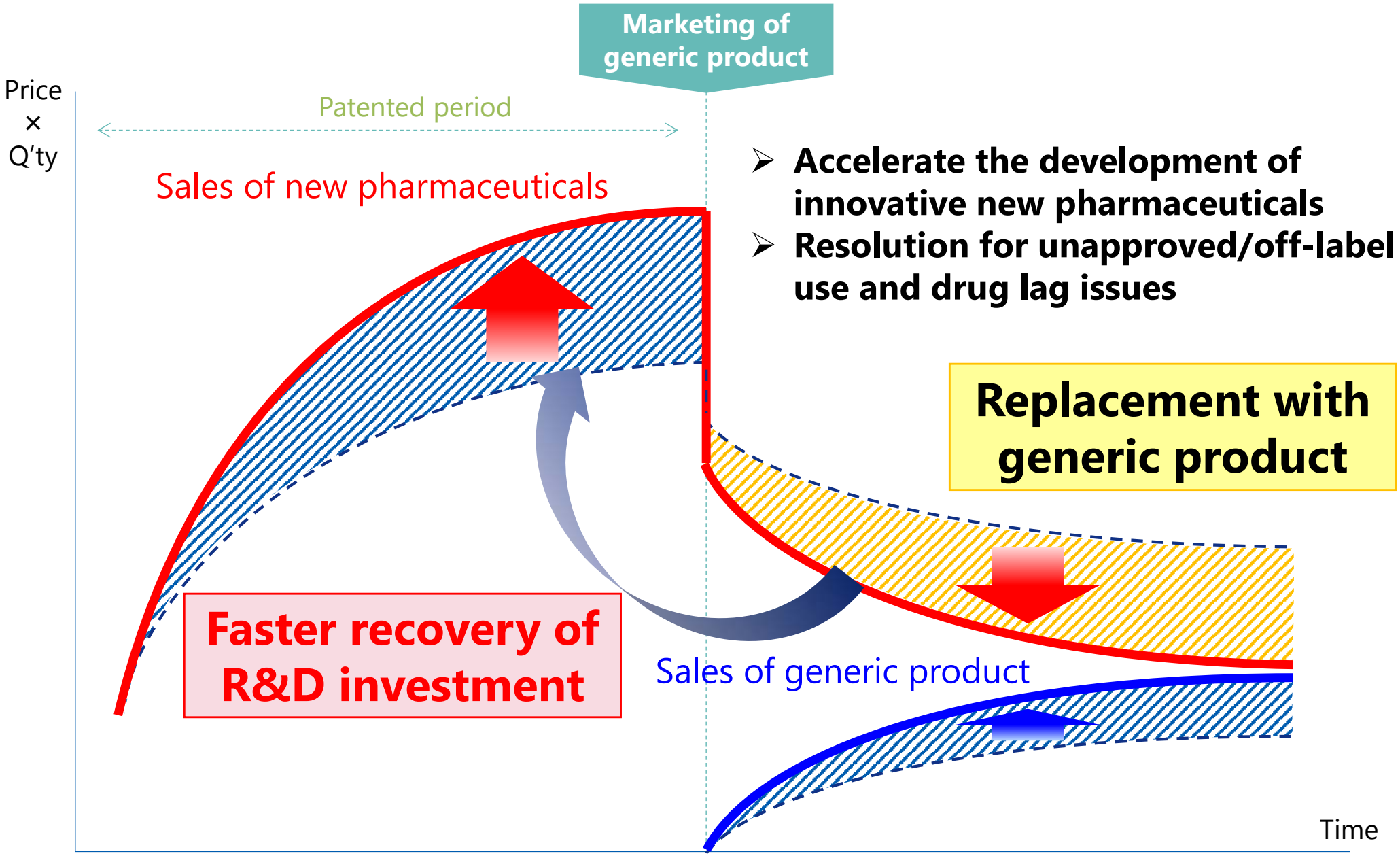
5. Listed products for which true clinical usefulness has been verified after marketing

- Drugs whose true clinical usefulness has been directly verified by the survey results accumulated after marketing and which have been published through publication, etc. in internationally reliable scientific journals

*However, this shall exclude cases where the burden on the marketing authorization holder is deemed to be fairly low, such as cases where the survey results serving as the basis of the survey have been obtained from research institutions such as universities.

Note)1. ~4. Not to be combined with each other (use the one with the highest premium rate)

Concept for new pharmaceuticals creation premium



- **Accelerate the development of innovative new pharmaceuticals**
- **Resolution for unapproved/off-label use and drug lag issues**

Exception of Low-priced Drugs, etc.

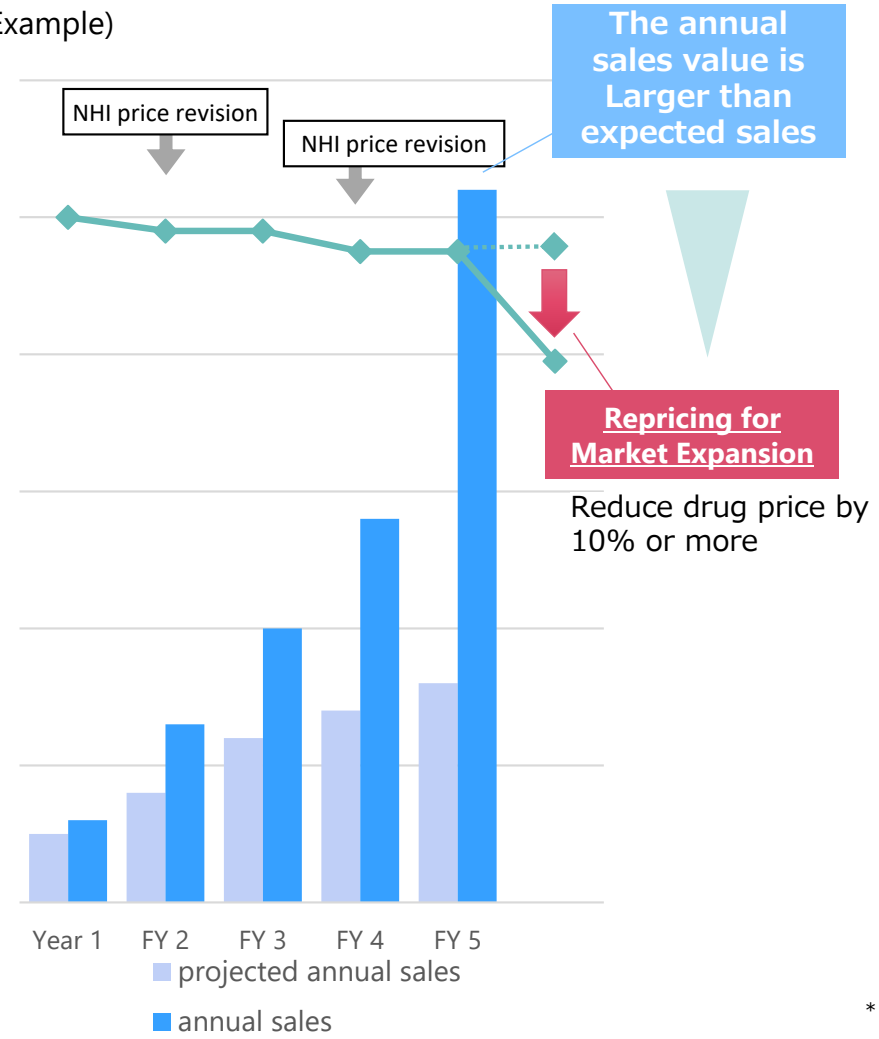
(1) Basic drugs	(Positioning of the system) • A system to support the drug price before the current recalculation of unprofitable products and the lowest drug price (Requirements of covered items) • Products with a high requirement for insured medical care • Products of which the efficacy and safety have been established as they have been widely used in clinical practice for a long period of time • Products that need to ensure the continuous and stable supply to the market (including repair of manufacturing facilities)
(2) Recalculation for unprofitable products	• Products with a high requirement for insured medical care • Products of which the minimum drug price has not been set, or which are unprofitable in the minimum drug price • Products difficult to be marketed continuously by the manufacturer due to significantly low drug price
(3) Minimum NHI price	• Price set for each dosage form regardless of ingredients to ensure the minimum cost of supply required for each dosage form

Repricing: Handling of Similar Products of Products Subject to Repricing for Market Expansion

Products (including products subject to reduction as similar products) for which drug prices have been reduced as a special case for repricing for market expansion shall be excluded from the reduction as similar products for repricing for market expansion (including special cases for repricing for market expansion) only once for a period of four (4) years from the day following the application of the reduction.

[Image of repricing for market expansion] Drug price reduction in case the annual sales value exceeds a certain multiple of the expected sales value, etc.

(Example)



Repricing for Market Expansion		Standard amount	Projected sales ratio	NHI price reduction rate	
				Cost accounting system	Price determination by comparable drugs
At the time of the drug price revision repricing	If the annual sales value exceeds a certain multiple of the expected sales value, etc., the price will be further reduced at the time of the drug price revision.	**Over 10 billion yen**	**≥ 10 times**	10~25%	-
		Over 15 billion yen	**≥ 2 times**	10~25%	10~15%
Repricing at times other than drug price revision (quarterly repricing)	For products for which additional indications, etc. have been approved, the price shall be revised according to the above formula taking advantage of the opportunity for new drug listing (4 times a year) only for products with a market size exceeding 35 bil. yen.	**Over 35 billion yen**	**≥ 2 times**	10~25%	10~15%
Special case repricing for market expansion (At the time of revision/quarterly)	Special case concerning handling of products with extremely large annual sales value	**100 ~ 150 billion yen**	**≥ 1.5 times**	10~25%	
		Over 150 billion yen	**≥ 1.3 times**	10~50%	

* Products subject to repricing for special case expansion or products similar thereto shall not be handled as products similar to repricing for market expansion or products similar to repricing for special case expansion even if they correspond to products similar to products similar to products for repricing for market expansion of other products only once during the period until the day four years elapse from the day following the date of application of the respective revision.

Cost-Effectiveness Evaluation System (Summary)

○The cost-effectiveness assessment system was introduced in April 2019 based on the discussion at Central Social Insurance Medical Council.
○Drugs and medical devices with a large market or a significantly high unit cost will be evaluated. However, this does not apply to rare diseases for which there are no sufficient treatment methods (e.g., designated intractable diseases) or products exclusively for pediatric use.
○The evaluation results are not used to determine the acceptability of insurance reimbursement but are used for price adjustment after listing in the insurance (supplement of the drug price system).
○In the future, the system will be improved, and case studies will be accumulated to discuss the ideal form of the system and how to utilize it.

[Cost-effectiveness evaluation procedure]

① Product Designation
(Designate drugs, etc. with a large market size

(2) Analysis by Company (-BL Feb - Sep (270 days))
Pre-analysis discussion (decision on framework of analysis, etc.), company analysis

③ Public analysis
(Verification) (March (90 days) to reanalysis (June (180 days)) (* 1)

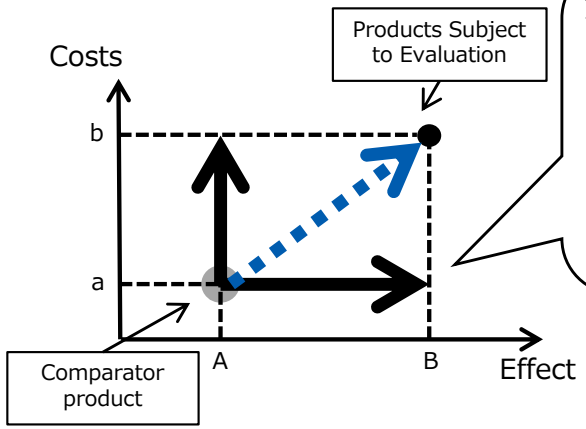
(* 1) Sponsored by the National Institute of Public Health

④ Overall Evaluation

(around Feb to Mar)

⑤ To cost-effectiveness assessments implement price adjustments based on

(Note)Periods in parentheses are standard intervals.

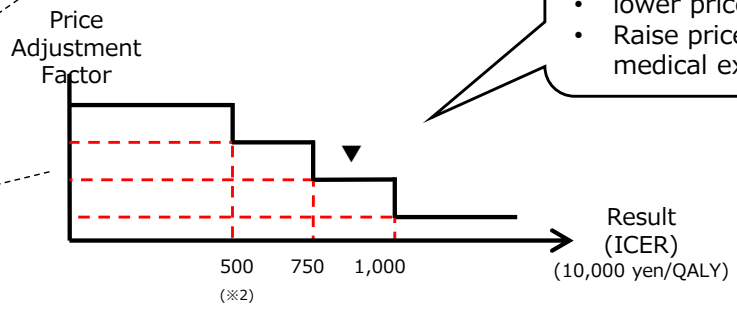


Analyze how much the cost and effect of the product subject to evaluation will increase compared to the comparator product (existing product).

Incremental cost-effectiveness ratio (ICER) = b-a (how much costs will increase) / B-A (increase in efficacy)

* Calculate the cost required to prolong 1-year survival in a healthy state.

In comprehensive evaluation, factors requiring consideration such as rare diseases, children, and anticancer drugs should be taken into consideration (* 2)



Adjust the price of the target product according to the evaluation results (* 3)
- lower prices for items with poor cost-effectiveness
- Raise prices for items, etc. that lead to a decrease in medical expenses

(* 2) For anticancer drugs, etc., a higher standard than usual (7.5 million yen/QALY) will be used.
(* 3) Price adjustment range includes utility premium etc.

Mechanisms for optimizing drug costs for "high-cost drugs."

1. Optimization of drug prices

(Example.)

Foreign Average Price Adjustment

From the viewpoint of ensuring fair market competition, price adjustments will be made in the cost accounting method etc., when there is a large deviation from foreign prices at the time of NHI price listing .

Market expansion re-calculation,

The price is reduced at the time of NHI price revision, etc., when the annual sales amount exceeds a certain multiple of the projected sales amount.

Cost-effectiveness evaluation

The target of the evaluation is a pharmaceutical or medical device with a large market size or significantly high unit price, and the cost and effectiveness of the target item are analyzed in comparison with existing comparative technologies. The price of the subject item is adjusted according to the results of the evaluation.

2. Optimization of use

(Example.)

Guidelines for Promotion of Optimal Use

For drugs with innovative new mechanisms of action, the "Guidelines for the Promotion of Optimal Use" were developed, which indicate the requirements for patients and medical institutions regarding the use of such drugs. The contents based on the guideline are notified as points to be considered for insurance coverage.

Guidelines for Promotion of Optimal Use (Requirements for target patients, setting of medica institutions-physicians)

For innovative and expensive drugs and cellular and tissue-based products, the use is optimized as follows.

- The pharmacological action and safety profile of drugs with innovative new mechanisms of action may be clearly different from those of existing drugs, and therefore the **Guidelines for Promotion of Optimal Use** was prepared showing the requirements for target patients and for medical institutions and physicians to use them. The contents based on the guideline were notified as points to consider for insurance application.
- Until sufficient information on efficacy and safety is accumulated, (1) **Use in patients who are expected to benefit strongly from the drug.** and (2) **Use at medical institutions meeting certain requirements so that necessary actions can be taken promptly when adverse reactions occur.**

< Number of Guidelines to Promote Optimal Use > *As of September 2021

	Total	Drug		Regenerative medicine products	
		New	Amend ments	New	Amend ments
FY 2016	3	3			
FY 2017	7	2	5		
FY 2018	12	4	7	1	
FY 2019	12	3	8	1	
FY 2020	11	2	8		1
FY 2021	13	4	5	3	1

< Flow of preparation >

Approval review (PMDA/MHLW) → **Approval** → Insurance listing procedure (MHLW) → **Insurance Coverage** → Cost-effectiveness assessments (MHLW)

(Within 60 days after approval in principle or within 90 days at the latest)

Examination of the optimal GLs (MHLW, PMDA, relevant academic societies, etc.) → **GLs formulation** → (Continuously reviewed. Revise as appropriate)

(Reference) Example of guidelines: Kymriah Intravenous Infusion

- Regenerative medicine products used for the treatment of relapsed or refractory leukemia, etc. Lymphocytes collected from the patient will be genetically modified and then intravenously administered to the patient. Approximately 34 million yen per patient (applicable on May 22, 2019)
- With the cooperation of academic societies and 8 medical associations, the optimal use promotion GL was prepared in parallel with the regulatory review, and the requirements for medical institutions and physicians, patients, etc. to be treated was specified. (Approved on March 26, 2019, issued on May 21, 2019)

< List of applicable drugs/regenerative medicine products >

Drug	Indications
Nivolumab (Opdivo Intravenous Infusion)	Malignant melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, head and neck cancer, gastric cancer, malignant pleural mesothelioma, esophageal cancer, and MSI-High colorectal cancer
Pembrolizumab (Keytruda Injection)	Malignant melanoma, non-small cell lung cancer, classical Hodgkin lymphoma, urothelial carcinoma, MSI-High solid cancer and colorectal cancer, head and neck cancer, renal cell cancer, esophageal cancer, breast cancer
Avelumab (Bavencio Intravenous Infusion)	Merkel cell carcinoma, renal cell carcinoma, urothelial carcinoma
Durvalumab (Imfinzi I.V. Infusion)	Non-small cell lung cancer, small cell lung cancer
Atezolizumab (Tecentriq I.V. Infusion)	Non-small cell lung cancer, breast cancer, small cell lung cancer, hepatocellular carcinoma
Alirocumab (Praluent Subcutaneous Inj.)	Familial hypercholesterolaemia, hypercholesterolaemia
Evolocumab (Repatha Subcutaneous Inj.)	Familial hypercholesterolaemia, hypercholesterolaemia
Dupilumab (Dupixent Subcutaneous Inj.)	Atopic dermatitis, bronchial asthma, chronic sinusitis
Omalizumab (Xolair Subcutaneous Inj.)	seasonal allergic rhinitis
Baricitinib (Olumiant Tablets)	atopic dermatitis

Drug	Indications
galcanezumab Emgality Subcutaneous Injection	Prevention of migraine attacks
Fremanezumab (Ajovy Subcutaneous Injection)	Prevention of migraine attacks
Erenumab (Aimovig Subcutaneous Injection)	Prevention of migraine attacks
Upadacitinib (Rinvoq Tablets)	Atopic dermatitis

Regenerative medicine products	Indications or performance
Human (autologous) bone marrow-derived mesenchymal stem cells (Stemirac Injection)	Improvement of neurological symptoms and functional impairment associated with spinal cord injury
Tisagenlecleucel (Kymriah Intravenous Infusion)	B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma
Axicabtagene ciloleucel (Yescarta I.V. Infusion)	Large B-cell lymphoma
Lisocabtagene maraleucel (Breyanzi IV Injection)	Large B-cell lymphoma, follicular lymphoma
Teserpaturev (Delytact Injection)	malignant glioma

Pharma Industry Vision 2021
—Pharma industry policies to promote healthcare and economic development together for safe and secure life— Key points

(Vision of the pharma industry policy)

○ Medicinal products are crucial to providing the Japanese people with extended healthy life expectancy and protection against health hazards. In addition, they also support economic activities, including consumption activities and labor participation. The pharma industry has contributed to the Japanese economy through its high tax-bearing capacity and employment.

○ The development of the knowledge- and technology-intensive pharma industry warrants scientific and technological improvement and innovation.

○ Thus, the following two will be achieved through the promotion of the pharma industry policies.

(1) Contribute to the extended healthy life expectancy in Japan through innovative drug discovery, as well as to the development of industry and economy through the improvement of capabilities in medical research and industrial technology as the world-leading advanced drug discovery country.

(2) Pass on the society where safe and quality medical care can be provided to future generations through the quality assurance and stable supply of medicinal products.

○ The prospects to collect adequate profits proportionate to investment in private sectors is crucial to realize these visions.

(Basic direction of the pharma industry policy)

○ Eight years have passed since the last Vision, and the environment surrounding the pharma industry has changed, for instance, drug discovery using the gene technology such as genomes or through data utilization, the spread of generic drugs, globalization of the pharmaceutical market and supply chains, fundamental reform of the prescription drug pricing system, and growing interest in vaccine and anti-infective agents.

○ The pharma industry policy will be developed by considering "economic security" and focusing on the following three issues to implement the visions mentioned above based on these changes.

(1) Innovative drug discovery: positively introduce seeds from academia and venture companies to meet unmet medical needs.

(2) Generic drugs: ensure the quality assurance and stable supply in response to the increasing medical necessity.

(3) Pharmaceutical distribution: achieve the stable supply and sound market formation to establish the environment where necessary medicinal products are available whenever necessary.

○ The MHLW's organizational structure for medicinal products should be strengthened to promptly and steadily promote such industry policies in ordinary and emergency times. The MHLW and related ministries will continue to discuss establishing the control tower function in the government noted as necessary to take comprehensive measures at all levels of the government.

○ Furthermore, key performance indicators (KPIs), such as "the number of medicinal products from Japan in the world's top 100 medicinal products in terms of sales volume," need to be set and evaluated, and, simultaneously, working-level communication between the public and private sectors and information dissemination should be continuously conducted to follow-up the visions and gain a public understanding for the pharma industry.

Challenges and directions of the pharma industry policies for each key theme

	Key challenges	Directions
Innovative drug discovery	- Increase of investment risks with an increase in levels of advancement and difficulty of research and development. - Necessity for utilization of data, including genome information, owing to the advancement of personalized medicine. - Concerns about lowering research and development capabilities of Japanese companies, as well as optimization and acceleration of research and development through the collaboration with venture companies and academia (the ecosystem). - Intensified efforts in overall healthcare sectors, including treatment methods other than medicinal products, prevention, and recurrence prevention.	- Public aids, injection of external funds, promotion of joint development, human resources training and employment, and support for overseas development to decrease the risk of investment and improve the investment environment [i-(1), (3), (4), (6), and (7), and ii-(1) and (4)] - Promotion of the improvement and utilization of medical information infrastructure, including genomes [i-(5)] - Construction of a global network with academia and venture companies (e.g., investment, alliance, and M&A) [i-(2) and (7)] - Improvement of the clinical study environment, including the construction of a network for regulatory harmonization and clinical studies in Asia [ii-(2)] - Ensuring transparency and predictability in the drug pricing system [ii-(4)]
Generic drugs	- Insufficient manufacturing and quality control and supply shortage at leading generic manufacturers. - Delay of the quantitative expansion of the Japanese market as the use percentage has reached almost 80%. - Promotion of appraisal by healthcare professionals to consider various elements other than prices. - Further acceleration of the lifecycles of medicinal products by considering biopharmaceuticals that are mainstream of blockbuster products.	- Enhanced responsibilities and control systems for stable supply based on the characteristics of generic products [ii-(5) and iii-(3)] - Support for overseas development, including generic drugs [v-(1)] - Improved transparency, including the disclosure of the status of stable supply and quality assurance [iii-(3)] - Promotion of use of generic drugs, including biosimilars [vi-(1)] - Promotion of selfcare/self-medication [vi-(2)]
Pharmaceutical distribution	- Improvement of the commercial distribution function based on the business practice (market price formation). - Increasing operations to respond to issues related to the physical distribution function, such as supply stop or recall.	- Promotion of the presentation of delivery prices based on values of medicinal products and the unit price-based, by-product negotiation [iv-(1)] - Early information acquisition on instable supply and consideration on a distribution scheme [iv-(2) and (3)]
Economic security	- Increase of shortage risks on supply chains owing to dependency on specific counties as sources of raw materials or products. - A legal positioning of responsibility for stable supply of medicinal products. - Reinforcement of the system for the development and production of vaccines and anti-infective agents.	- Risk analysis of Stable Supply Drugs and reinforcement of the supply chains [iii-(1) and iv-(2) and (3)] - Thorough administrative guidance for stable supply, establishment of mechanisms of information collection and disclosure on short supply, and discussion on the legal positioning of responsibility for the stable supply [ii-(5)] - Ensuring profitability and predictability of vaccines and anti-infective agents (including AMR) [i-(1), ii-(3) and (4), and iii-(2)]

*** Besides the above, a discussion should be conducted regarding, for instance, the promotion of public understanding of medicinal products and continued communication between the public and private sectors, as well as reform of the MHLW's organizational structure.**

Specific measures to be implemented in each phase

i Research and development

(1) Determination of priority areas and accompanying support

Determination of prioritized support per the levels of the advancement of medicinal products and one-stop accompanying support for high-priority areas or fields, including vaccines and anti-infective agents.

(2) Arrangement of research and development environment focused on the creation of open innovation community

Organization of an open innovation community to maintain domestic research and development capabilities and invite overseas venture companies.

(3) Enhancement of research and development capability through human resources

Efforts to train and employ bioinformaticians through the industry–government–academia collaboration and diversification of research evaluation methods in the academia.

(4) Risk money supply and matching support

Reinvigoration of the inflow of public and private funds for the priority areas to support practical development and creation of a platform for research results matching.

(5) Development of research and development data infrastructure

Promotion of standardization of information necessary for research including steady implementation of “Whole-genome analysis implementation plan,” utilization and preparation of guidelines for the use of medical information, consideration of a legal system for their protection and utilization, improvement of the practicality of each data infrastructure, public accountability on objectives and results of information use, support for optimizing the selection of new drug candidates by AI, and sharing of expensive research facilities.

(6) Support for intellectual property strategy development

Implementation of research by public and private sectors to establish an intellectual property strategy in response to the advancement of technologies based on the characteristics of biopharmaceuticals.

(7) Enhancement of research and development investment

Support to enhance investment in research and development by considering an increase in research and development costs and a decrease in success probability.

ii Regulatory approval/NHI price listing

(1) Establishment of regulatory science

Early establishment of the regulatory science, which is a prerequisite of consistent support for priority areas, while listening to opinions from researchers and developers.

(2) Improvement of clinical trial environment

Promotion of participation in clinical studies by providing easy-to-understand clinical study information and reducing patients’ burden, the establishment of bases such as clinical research core hospitals, promotion of training and collaboration of experts in various fields, and facilitation of joint clinical studies in Asia to streamline the entry into Asian markets.

(3) Acceleration of regulatory approval process and development of standards in case of emergency

Preparation of a clinical study frame protocol in emergencies per the international consensus, consideration on further utilization of overseas clinical study data at the time of approval review and a system to allow for special use of such data in emergencies, and consideration of acceleration and simplification of the national test of vaccines.

(4) Ensuring transparency and predictability in the drug pricing system

Consideration of evaluation of innovation, improvement of transparency of cost calculation methods, reinforcement of the system for consultation with the MHLW at an early stage, optimization of the implementation processes of routine immunization, and introduction of pull-type incentives and a purchase system by the government in case of emergency.

(5) Reinforcement of responsibility of generic drug companies for stable supply

Verification of the management system proportionate to the numbers of types and the volume of products to be manufactured, considering the high-mix manufacturing at a stage of approval or GMP conformity inspection, review of joint development, including reinforcement of accountability of data at a development stage and a lineup of specification, thorough verification of stable supply at the NHI price listing, refusal to the NHI price listing in case of supply instability, consideration of a legal positioning of responsibility for the stable supply, consideration of the establishment of mechanisms of information collection and publication on short supply.

iii Manufacturing

(1) Reinforcement of supply chain from the viewpoint of security

Grasping the supply chains of high-priority Stable Supply Drugs, investigation of structural risks and the strategical essentiality, requests to pharmaceutical companies for increasing product inventories or using multiple sources, domestic manufacturing support/stockpile systems, and drug price incentive to cover costs necessary for the stable supply, and consideration of pull-type incentives.

(2) Establishment of manufacturing bases for biopharmaceuticals and regenerative medicine products

Establishment of the production system with global quality, training for talents in bioscience through the industry–government–academia collaboration, support for facilities renovation of vaccine manufacturing facilities, the establishment of manufacturing base facilities such as dual-use facilities, improvement of facilities from the viewpoints of physical distribution to facilitate the international deployment, fostering of technologies and human resources, and reinforcement of domestic production development of media and materials aiming at the international deployment and de facto standard establishment.

(3) Monitoring and transparency improvement of the manufacturing control system for generic drugs

Strict GQP quality control at marketing authorization holders, disclosure of the status of efforts and performance of stable supply and quality assurance at each company, and consequent appropriate market formation, and unannounced inspection of nonconforming products in sample collecting investigation.

iv Distribution

(1) Supporting wholesaler negotiations

Improvement of guidelines for distribution improvement and its education and dissemination to allow appropriate price negotiation, including the unit price-based by-product negotiation.

(2) Early detection of information on supply instability and countermeasures

Knowing supply instability in advance through information exchange with overseas regulatory authorities, consideration of how to provide information of supply shortage cases, consideration of a scheme to determine distribution stock in emergencies regarding high-priority Stable Supply Drugs, and consideration of terms of distribution regarding vaccines, infusions, blood products, herbal and Chinese medicines, and topical products for which the stable supply is required.

(3) Preparation during ordinary times aiming at the collaboration in emergencies

Consideration of a scheme for distribution in case of supply instability and preparation of BCP of wholesalers.

v International deployment

(1) Support for deployment in the areas with expanding markets

Promotion of regulatory harmonization and the universal health coverage (UHC) in Asia and other regions; reinforcement of collaboration with the PMDA, government offices abroad, the JETRO, and international organizations; and information provision and support regarding the prequalification (PQ) of the World Health Organization (WHO) or international public procurement markets.

vi Others

(1) Promotion of the use of generic drugs, including biosimilars

Utilization of formulary, appreciation of biosimilar prescription in the medical service fee system, and goal-setting and dissemination/publicity of biosimilars.

(2) Maintenance and improvement of the public health level with OTC drugs

Improvement of health literacy through the reinforcement of health consultation by family physicians and pharmacists and health support function of the pharmacy; spread and establishment, efficacy verification, and selection of applicable products for the self-medication taxation system; and diversification of options for the Japanese people by promoting switching to OTC with assured safety and efficacy.

* Promotion of public understanding of medicinal products.

Continuous implementation of working-level communication between the public and private sectors and promotion of public understanding through the information transmission regarding the social values of medicinal products and the pharma industry, as well as the research and development and the stable supply of medicinal products.

* Establishment of a system to promote the pharma industry policies.
  - Reform of the MHLW's organizational structure for medicinal products.
  - The MHLW and related ministries will continue discussing the establishment of the control tower function in the government noted as necessary.

(Reference) KPI to follow-up the pharma industry policies

○ Several KPIs should be continuously measured to check the progress of the pharma industry policies.

○ For instance, while the following KPIs could be used for innovative drug discovery, specific KPIs should be discussed through working-level communication between the public and private sectors.

- The number of medicinal products from Japan in the world's top 100 medicinal products in terms of sales volume.
- Rank of the Japanese market in the launch order of each drug that is ranked high in global sales, as well as the time lag for their launch.
- Overseas sales of Japanese companies.
- Balance between in- and out-licensing in the pharmaceutical industry in Japan.
- Research and development expenditures of pharmaceutical companies.
- The number of seeds licensed out from academia and venture companies, that of clinical studies based on such seeds, and that of product patents resulted from such seeds.
- Manufacturing capacities of biopharmaceuticals in Japan and overseas.