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## 6. Medical Drugs/Medical Devices

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# 6.1 Medical Drugs/Medical Devices | Pharmaceuticals

## **Definition of New Drugs**

New Drugs (Originator drugs) are medical drugs which are clearly differentiated in active ingredients, dosage, administration, indication and efficacy from drugs which have already been approved. New Drugs mainly consist of drugs containing new active ingredients, new ethical combination drugs, drugs with a new administration route, drugs with a new indication, drugs in new dosage forms, and new dosage drugs.

## **Pharmaceutical Product Approvals**

To manufacture, distribute and sell new drugs, pharmaceutical companies must first obtain marketing approval from the PMDA. Approvals are made by the PMDA based on an evaluation of the new drug's efficacy and safety information obtained via clinical trials. Clinical trial information and filing documents must conform to the quality, GLP and GCP requirements defined by the MHLW.

In addition to the standard approval process, the MHLW has implemented mechanisms for expedited reviews and approvals of innovative pharmaceutical products.

To address the development lag between Japan and other major markets, the MHLW implemented the "Sakigake" review policy in 2014 that awards prioritized reviews and expedited approvals for products that are developed for and filed for first in Japan. To be eligible for "Sakigake" reviews, new drugs must meet all of the following criteria: 1) innovative new mechanism of action, 2) degree of severity of the target indication, 3) high degree of effectiveness, and 4) a desire to develop and file first in Japan.

Furthermore, in 2017, the MHLW implemented the "Conditional Expedited Approval" Policy for drugs that address disease states with small patient populations with limited treatment options and large unmet medical needs for which the execution of confirmatory clinical trials are difficult. The policy enables pharmaceutical companies to file for approval with efficacy and safety data generated from non-confirmatory trials, such as phase II trials, on the condition that additional safety and surveillance measures, including the use of real world data, are implemented. It is expected that this policy will support the development of novel treatments including iPS cell based genetic therapies.

## **Pharmaceutical Reimbursement Pricing**

Once marketing approval is obtained, manufacturers must apply for reimbursement pricing under the National Health Insurance (NHI) system. The NHI reimbursement price is the price at which payors reimburse medical institutions for pharmaceutical products used to treat patients.

Initial NHI Reimbursement prices that are set by the MHLW's Central Medical Council based primarily on the comparable based method when similar approved products already exist on the market, or the cost based method for novel therapeutics with no similar approved products.

In addition, the MHLW has also implemented pricing premiums to both incentivize the development of innovative products while constraining the reimbursement prices of products whose degree innovativeness are assessed to be limited. Products with superior efficacy or usefulness compared to existing products, with orphan or pediatric indications, or for which Japan is the first country are eligible for additional price premiums, whether priced via the comparator or the cost based methods

Once set, pharmaceutical reimbursement prices are revised biannually based on an assessment of the variance between NHI reimbursement prices and actual market (wholesale) prices. While the price difference between NHI reimbursement prices and actual market prices enable medical institutions and pharmacies to book revenue, biannual price revisions are intended to limit discounting to within a reasonable range known as the "R-zone" established by the MHLW, currently set at 2% of reimbursement prices. In practice, the biannual price revisions have the effect of lowering drug prices, enabling the MHLW to control the natural growth in overall healthcare spending.

In addition to the standard biennial reassessment of drug prices in Japan, additional adjustments have also been implemented to ensure products are profitable and to promote the development of new drugs while limiting overall costs by reducing prices for drugs that have seen significant market expansion or that have lost patent protection.

Adjustment	Type	Description
Lack of profitability	Positive adjustment	<ul style="list-style-type: none"> <li>Unprofitable drugs with high medical need are eligible for an increase in NHI list price by MHLW or generics where all generic products are unprofitable</li> </ul>
Market size expansion	Negative adjustment	<ul style="list-style-type: none"> <li>Added price cuts for increased market size or sales due to indication expansion</li> </ul>
Premium to promote the development of new drugs and eliminate off-label use	Positive adjustment	<ul style="list-style-type: none"> <li>Premiums for innovative products designed to slow price reductions and promote new drug development</li> </ul>
Additional Cuts for Long Listed Drugs	Negative adjustment	<ul style="list-style-type: none"> <li>Additional cuts to long listed products</li> <li>Used to fund premiums for new drug development</li> </ul>

As healthcare costs continue to rise, it is expected that additional revisions to pharmaceutical reimbursement pricing mechanism may be made going forward. While undetermined, to date, topics such as the introduction of health economics outcome considerations when setting reimbursement prices in addition to potential shift towards annual price revisions have been discussed.

### **Pharmaceutical Product Quality and Safety**

Similar to other major markets, the development, manufacture and distribution of pharmaceutical products in Japan are also governed by GXP regulations such as GLP, GCP, GMP and GVP standards. However, there are a few notable differences in Japanese regulations and policies related to product quality and safety.

First, under the Pharmaceutical Affairs Law, to comply with Japan’s Good Quality Practices (GQP) and GVP requirements, pharmaceutical companies must designate three individuals to take on the following roles unique to Japan to oversee and govern product quality and safety related activities:

- General marketing compliance officer – Individual with overall responsibility for product quality and safety
- Quality assurance manager – Individual responsible to ensure quality activities comply with GQP regulations
- Safety manager – Individual responsible for ensure safety activities comply with GVP regulations

Second, upon approval of novel drugs, Japan requires pharmaceutical companies to conduct post marketing surveillance activities to track and ensure patient safety. Surveillance activities are generally required to be conducted during the 6 month period after launch and are intended to identify track any adverse events in the real world setting that may not have been observed during clinical trials. These activities are governed by Japan’s Good Post-marketing Surveillance Practice (GPSP) regulations.

Third, to further ensure patient safety, new pharmaceutical products are generally restricted to 14 day prescriptions for one year from the first day of the month pricing is listed. Exceptions to the 14 day prescription restriction for specific new drugs can be awarded by the Central Medical Council for products that meet either of the following two criteria:

- New drugs (e.g. compound drugs) with APIs that have the same effect, efficacy, dosing and administration as approved products with over one year of clinical experience
- New drugs where, based on its characteristics or the disease state, only over 14 day formulations exist and the safety of over 14 day administration has been confirmed

# 6.2 Medical Drugs/Medical Devices | Generic Drugs

## Definition of Generic Drugs

Medical drugs have a period when the pharmaceutical company which first developed it has the exclusive rights for manufacturing and marketing them (period during which patent is in effect and reevaluation period for verifying efficacy and safety), and the drugs manufactured and marketed during this period are called original drugs.

Once this period expires, based on the publicized patent information, other pharmaceutical companies can manufacturer/market drugs which contain the same active ingredients. These drugs thus launched which contain the same active ingredients as the original drug are called generic drugs.

The characteristics of generic drugs are that while they have the same active ingredients and as a general rule the same efficacy, effect, dosage and administration as the original drug, their prices are lower. Also, while the original drugs are exclusive to the pharmaceutical company which developed it first, in many cases, generic drugs are manufactured and marketed by several pharmaceuticals. In the Western market, as these drugs are often prescribed using the generic names of the active ingredients (as opposed to original drugs which are often called by their brand names), they have been called generic drugs, and this term has become popular in Japan as well.

### Efficacy and Safety of Generic Drugs

To manufacture and market generic drugs, unlike the original drug, there is no need to conduct clinical trials to verify efficacy and safety of the active ingredients, as efficacy and safety have already been established in the approval process of the original drug.

However, even if the drug has the same active ingredients, if it is made by a different manufacturing process, it may not have the same mode of action. Therefore, in the manufacturing and marketing of generic drugs, they are examined to see if the efficacy and safety are equivalent to those of the original drug. Evaluation criteria consist of “Test Procedures and Acceptance Criteria”, “Stability Test”, “Bioequivalence Studies”. If, based on these criteria, the generic drug is proved to be the same as the original drug, its efficacy and safety are cleared of any issues and the generic drug is eligible to get approval.

### Perspective: MHLW’s position on generic drugs

In Japan, thanks to the universal national health insurance system, every citizen has equal access to a necessary and high quality medical treatment by paying only a certain percentage of the medical cost from his/her own pocket. On the other hand, with the advancement of medical technology and fast-aging society, Japan’s healthcare cost keeps on rising increasingly jeopardizing the sustainability of the national healthcare system. To maintain this universal healthcare system, sustain the quality of medical care and to drive efficiency improvement in the healthcare service, Japanese government has adopted a policy to encourage the usage of generic drugs.

In the cabinet decision in June 2015, it has set a target to achieve the share of generic drugs of 70% by 2017 and 80% by September 2020, with an ambition to achieve these targets as soon as feasible.

## Prescription and Dispensing of Generic Drugs

In Japan’s National Health Insurance System, when physicians prescribe medical drugs, it is a common rule to use the generic name of the active ingredient. However, a physician can choose to put his signature on his prescription to specifically request the pharmacist to dispense original drug and not to change to generic drugs. Pharmacies, unless there are specific instructions from the physician, are encouraged to dispense generic drugs upon briefing to the patient and getting his/her consent. Incentives are set to make sure pharmacies will proactively choose to dispense generic drugs.

France is another market which adopts a similar mechanism of prescription and dispensing of generic drugs. In France, if a pharmacy refuses to dispense generic drugs in substitution to the original drug, the patient has to

pay 100% out-of-pocket at the pharmacy and apply for reimbursement later. This system is a strong incentive to drive penetration of generic drugs.

USA is an example of a market which adopts a different system than Japan. In the USA, the insurance policy held by the patient dictates which medical drugs he can use, giving limited freedom of choice to the physician or the pharmacist. The decision of which drug is to be adopted is made by the HMO, the insurer, in negotiation with the pharmaceutical company.

### **Drug Price of Generic Drugs**

As generic drugs don't require clinical trials and relieves the pharmaceutical company of large chunks of R&D expenses compared to an original drug, pharmaceutical companies can remain profitable even if the drugs prices are set lower than the original drugs. For this reason, in Japan's National Health Insurance System, it is a common practice that the reimbursement price of generic drugs is set significantly lower than that of the original drug, generally at 50% or less.

Furthermore, in Japan's NHI system, reimbursement prices are determined by taking actual market prices into consideration. Therefore, if several generic drugs which contain the same active ingredient exist in the market and price competition occurs in the market, cheaper reimbursement price will be set reflecting those circumstances.

### **Rules for Determining NHI Listed Price of Generic Drugs**

Twice in a year (June and December), generic drugs have opportunities to get screening for approval and inclusion in the NHI reimbursement list.

If generic drugs are to be included in the NHI list for the first time, the basic rule is to set its price at 50% of the original drug, with two exceptions: the price of internal medicine is set at 40% of the price of the original drug if the number of items proposed for inclusion in the NHI list exceeds 10 items; and price of biosimilar is to be set at 70% of the original drug.

Furthermore, after the initial inclusion in the NHI list, drug prices will be gradually reduced at each of the biannual drug price revision which target all listed products in the NHI list, according to the changes in the actual market price. In cases where several generic drugs exist, a policy is implemented for setting one price per each price range, as described below:

- Generic drugs whose price is estimated to be less than 30% of the highest price are included in the list at single price (weighted average)
- Generic drugs whose price is estimated to be 30% or higher but less than 50% of the highest price are included in the list at single price (weighted average)
- Generic drugs whose price is estimated to be 50% or higher of the highest price are included in the list at single price (weighted average)

# 6.3 Medical Drugs /Medical Devices | Non-prescription Drug

## Segmentation of prescription drugs and non-prescription drugs

Apart from prescription drugs which are dispensed by the pharmacist and taken by the patient according to the prescription issued by a physician/dentist, drugs requiring guidance and non-prescription drugs exist which general public may purchase directly at pharmacies and drugstores and use at one’s own discretion.

As non-prescription drugs can be purchased/taken by the general consumer at his/her own discretion, sellers are required to provide information to the buyer, and they are divided into Class 1, Class 2 and Class 3 based on risk level, each category with a defined degree of necessity of providing information.

- Class 1 Drugs : Drugs for which pharmacists are required to provide information and only under a pharmacist’s management and guidance can be sold/handed over
- Class 2 Drugs :Drugs which can only be sold and handed over at stores where pharmacists/registered sellers are working full time, and providing information has to be done on best effort basis.
- Class 3 Drugs : Drugs whose risk level is the lowest. Unless the buyer directly requests for it, they can be sold without any legal obligation to provide explanation in particular.

Drugs requiring guidance are, distinct from non-prescription drugs, categorized as “quasi-prescription drugs”, and Switch OTC Drugs, which have just been switched from prescription to non-prescription drug and thus haven’t been certified risks as non-description drug, as well as Direct OTC Non-prescription Drugs, which have never been used as prescription drugs, fall into that category.

OTC Drug Categorization		Expert	Explanation from Salesperson to Customer	Response to Customer Request for Consultation	Distribution on the Internet/Mail-order
Behind-the-Counter Drug		Pharmacist	Provide written information face-to-face (Obligation)	Obligatory	Not permitted
Non-prescription Drug	Category1		Provide written information (Obligation)		
	Category2	Pharmacist or registered sales person	Best efforts		Permitted
	Category3		Not stipulated in law		

The term "OTC pharmaceutical" refers to pharmaceuticals without any significant action on the human body in terms of its efficacy and effect, intended for use with options selected by a consumer based on information provided from a pharmacist and other medical professionals.

# 6.4 Medical Drugs/Medical Devices | Medical Devices

## Medical Device Classification and Approval

In Japan, medical devices are defined as approved medical products with clearly defined structure, method of use, effect and performance to be used with objective of either “diagnosing, treating or preventing disease” or “impacting the structure or function of the human body.”<sup>1</sup>

Medical devices, in Japan, are classified into the following four categories based on their intended use and safety risk. Approval requirements for medical devices vary by category

In particular, category III and IV medical devices with the largest risks require PMDA approval.

Category		Type of Medical Device	Approval Requirement
General Medical Devices	Class I	Medical devices with extremely low risk in the event of defect / failure: <ul style="list-style-type: none"> <li>• Enteral infusion sets, nebulizer, x ray film, blood gas analyzer, surgical non-woven products, etc.</li> </ul>	<ul style="list-style-type: none"> <li>• Self declaration</li> </ul>
Controlled Medical Devices	Class II	Medical devices with relatively low risk in the event of defect / failure: <ul style="list-style-type: none"> <li>• X-ray imaging device, electrocardiograph, ultrasonic diagnostic device, injection needle, blood collection needle, vacuum blood collection tube, infusion set for infusion pump, Foley catheter, hearing aid, household massager, etc.</li> </ul>	<ul style="list-style-type: none"> <li>• Third Party Certification</li> </ul>
Specially Controlled Medical Devices	Class III	Medical devices with relatively high risk in the event of defect / failure: <ul style="list-style-type: none"> <li>• Particle beam therapy equipment, artificial dialyzer, epidural catheter, infusion pump, automatic peritoneal perfusion device, artificial bone, artificial heart-lung machine, artificial respirator, etc.</li> </ul>	<ul style="list-style-type: none"> <li>• Minister’s Approval</li> <li>• Third Party Certification</li> </ul>
	Class IV	Invasive medical devices with life threatening risk in the event of defect / failure: <ul style="list-style-type: none"> <li>• Pacemaker, coronary stent, artificial blood vessel, PTCA catheter, central venous catheter, etc.</li> </ul>	<ul style="list-style-type: none"> <li>• Minister’s Approval</li> </ul>

<sup>1</sup>The Japan Federation of Medical Devices Association "On Medical Equipment" <http://www.ifmda.gr.jp/device/about/> (Accessed 2018, Apr. 30)

### Medical Device Reimbursement Assessment Categories

Under Japan's insurance scheme, the manner in which medical devices are reimbursed and priced depends on its reimbursement assessment category<sup>2</sup>

- Medical devices within the A1, A2, and A3 categories covered within the technical fee for specific procedures and cannot be reimbursed separately
- Medical devices within the B1, B2 and B3 categories are referred to as Specialty Treatment Materials that are directly reimbursed separately from technical fees based on reimbursement prices set by technical category
- Medical devices within the C1 and C2 categories are, similar to B category devices, directly reimbursed separate from any technical fees. However, as they do not fit existing technical categories upon approval, the creation of a new technical category is required. Furthermore, C2 medical devices also require the creation of a new technical category as well
- B3, C1 and C2 medical devices require approval by the Chuikyo

Assessment Category		Reimbursement Method
A1	Comprehensive	Items covered by the technical fee
A2	Specifically Comprehensive	Items that are covered by existing, specific technical categories
A3	Existing Technology w/revision	Items that are covered by existing, specific technical categories (Require changes to consideration items)
B1	Existing Technical Category	Specialty Treatment Material that is directly reimbursed based on existing technical category separately from technical fees
B2	Existing Technical Category w/ revision	Specialty Treatment Material that is directly reimbursed based on existing technical category separately from technical fees (Requires revision of existing technical category)
B3	Fixed Period Enhancement Premium	Specialty Treatment Material that is evaluated by awarding temporary premiums based on existing technical category
C1	New Function Product	Products that need a new function classification and have already been evaluated for technical fee
C2	New Function / Technology Product	Products that need a new function classification and have not yet been evaluated for technical fee
F	Not suitable for NHI reimbursement	

### Reimbursement Prices for New Medical Devices

Unlike pharmaceutical products which are reimbursed by product, medical devices are reimbursed based on the technical category.

New medical devices are priced either via the "comparable technical category method" if there is an existing technical category exists for similar products, or via the "cost based method" when there is no existing technical category. Medical device reimbursement prices are revised concurrently with the periodic reimbursement revisions.<sup>3</sup> Similar to pharmaceutical products, medical device price revisions are decided primarily on the variance between the reimbursement price and actual market prices based on an acceptable margin including consumption tax of 4%.

<sup>2</sup> Ministry of Health, Labour and Welfare "Outline of the 2018 Revision of the Medical Products and Equipment Insurance System" <https://www.idta.org/pdf/20180404-3.pdf> (Accessed 2018, May. 1)

<sup>3</sup> Ministry of Health, Labour and Welfare "2016 Revision of the Medical Products and Equipment Insurance System" <http://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000114377.pdf> (Accessed 2018, Apr. 30)



In addition, the MHLW has also implemented medical device reimbursement pricing policies to promote innovation.

- Challenge Filing: Mechanism to subsequently file for a new technical category post approval based on real world data
- Fixed Period Enhancement Premium: Additional price premium awarded for 2 reimbursement periods to products able to replace an existing technical category
- Technical Category Exception: Mechanism applied to highly innovative or Sakigake products in which prices are maintained at a higher level for 2 reimbursement periods separately from other follow on products within same technical category

Going forward, similar to pharmaceutical products, to control reimbursement prices, it is expected that health economics outcome considerations may also be considered when deciding medical device pricing.<sup>4</sup>

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<sup>4</sup> Ministry of Health, Labour and Welfare "Outline of the 2018 Revision of the Medical Products and Equipment Insurance System"  
<https://www.jdta.org/pdf/20180404-3.pdf> (Accessed 2018, May. 1)