Asia-Pacific
Economic Cooperation

2022/SOM3/IPEG/WKSP2/007

Patent Linkage System in Japan: Framework, History and Impacts

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THAILAND

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Patent Linkage System in Japan :
Framework, History and Impacts

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   - Mechanism of a new drug and the generic market
     - Examples of institutional factors to balance between both markets
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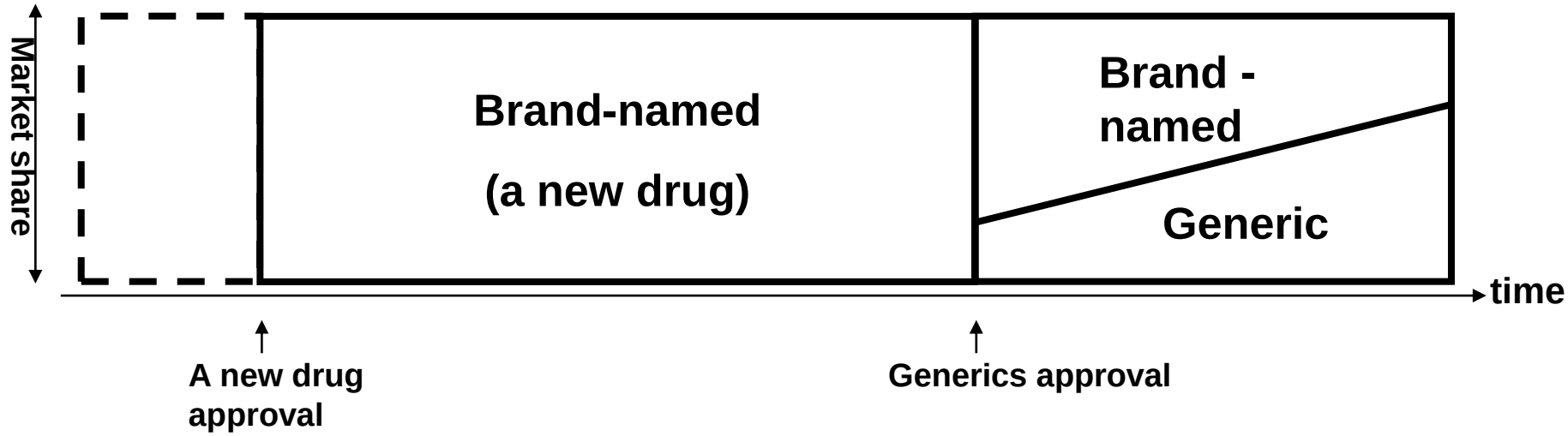
   - Is the Japanese system “Patent Linkage” ?

Mechanism of a New Drug and the Generic Market

Examples of institutional factors to balance between both markets



Incentive to R&D for a new drug

Recoupment of huge investment

VS

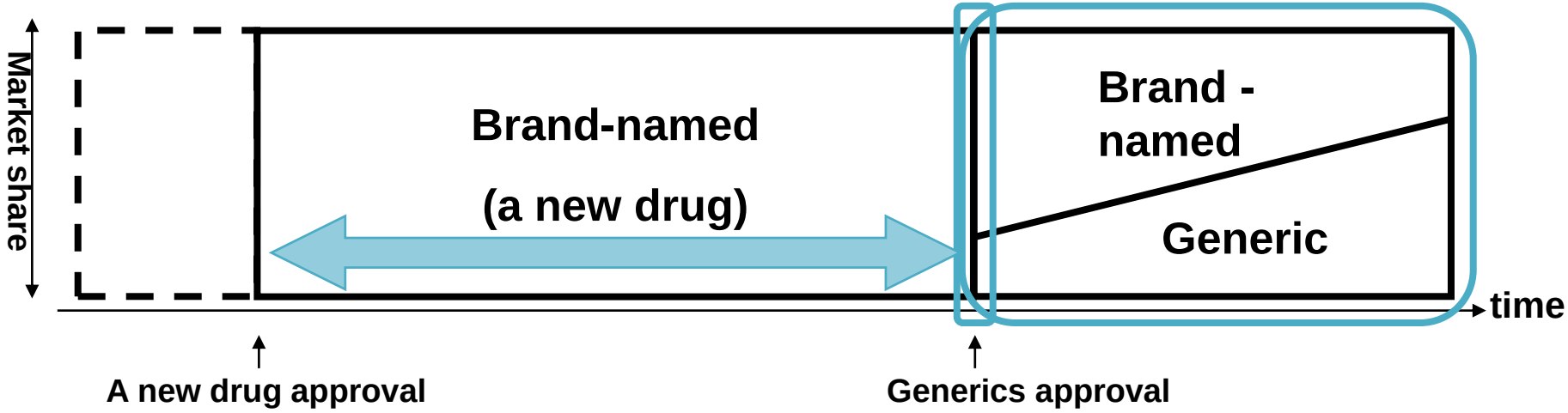
Protection for public health

Affordable & available drugs

How do we find a balance?

Mechanism of a New Drug and the Generic Market

Examples of institutional factors to balance between both markets



1. **Control of the monopoly period for a new drug by IP protections**
   - Patent protection (product patent, patent term extension)
   - Data protection against a generic application
2. **Control of generic approval process under patents of a new drug**
   - Bolar provision (Experimental use exception)
   - Patent Linkage System
3. **After generics enter;**
   - Drug price system, reimbursement system
   - Distribution structure / business practice etc.

Mechanism of a New Drug and the Generic Market

Examples of institutional factors to balance between both markets

		Japan	The US
Patent Term Extension	Basis provision	**Patent Law 67.2**	**35USC § 156**
	Extension term	• 5 years (at most)	• 5 years (at most) • (14 years of the monopoly period)
	Extension occasion	• Each approval for new drug application (including indications) • Each patent	• One time for NME • One patent
Data Protection against Generics (Re-examination period)	Basis provision	**Pharmaceutical Affairs Law 14-4** (Re-examination period) • PFSB Notification No.1121-2 (November 21, 2014)	**21USC § 355A, E, (j)(5)(B)** (Market exclusivity period)
	Protection term (for NME)	• 8 years ＊the same for Biologics	• 5 years ＊12 years for Biologics
	Protection term (for Orphan)	• 6～10 years • Within 10 years (pediatric)	• 7 year • +6 months(pediatric) • +5 years(specific antibiotic)
	Protection term (for Others)	• 6～8 years (revolutionary) • 4 years	• 3 years

"In case of the application of a drug which is recognized as equivalent of the original drug in respect to its ingredients and amount, dosage and administration, and efficacy in the re-examination period of the original drug, the same materials as the original drug or more is required for the drug approval."

PFSB Notification No.1121-2 (November 21, 2014)

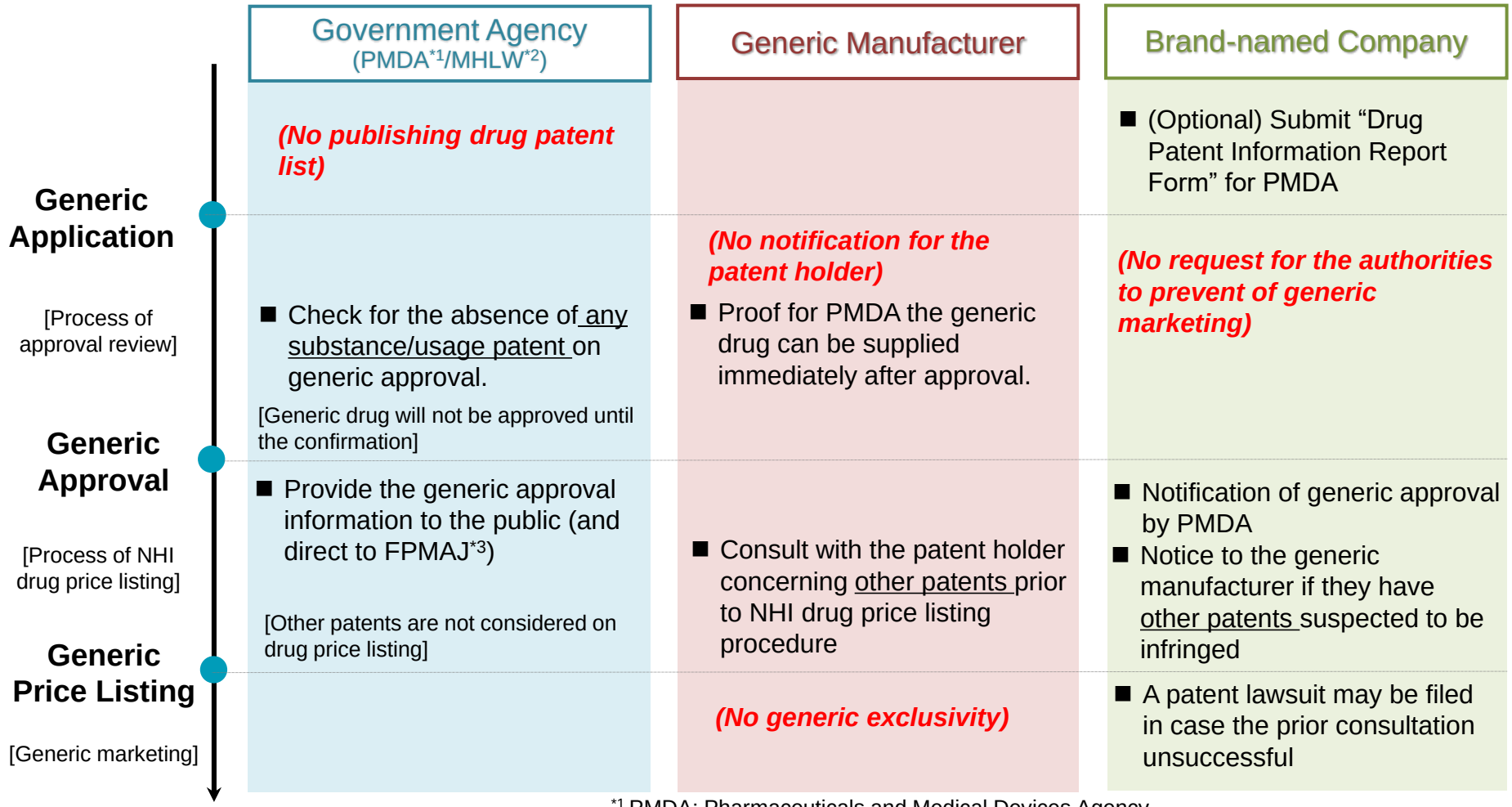
Mechanism of a New Drug and the Generic Market

Examples of institutional factors to balance between both markets

		Japan	The US
Experimental use exception (Bolar provision)	Basis Provision	**Patent Law 69.1** ”experimental and research”	**35USC § 271(e)(1)** “solely for uses reasonably related to the development and submission of information”
	Tests for generic approval	• Applicable • *Supreme court (April 16, 1999)*	• Applicable
	Tests for a new drug approval	• Applicable • *IP High court (February 9, 2021)*	• Applicable • *Roche Prods. v. Bolar Pharmaceutical Co., 733 F.2d 858* • *Merck KGaA v. Integra Lifesciences I, Ltd., 245 U.S*
Patent Linkage	Basis Provision	• Notification No.765 of PE/PAB (October 4, 1994) • Notification No.0605001 of EA/HPB & No.0605014 of PE/PFSB(June 5, 2009)	**21CFR§314.53, 94, 07** **21USC§355(J)(2),(5)**
	Before Generic application	• Reporting of drug patent Information (optional)	• Registration of a patent list • “Orange Book”
	In Generic Approval Review	• Checking for the absence of substance/usage patents • Proof of immediate supply after approval	• Notice of generic application in Paragraph(IV) • Automatic 30 month stay of generic approval by patent litigation
	After Generic Approval	• Prior consultation concerning other patents before NHI drug price listing	• 180 days of market exclusivity for the first generic applicants

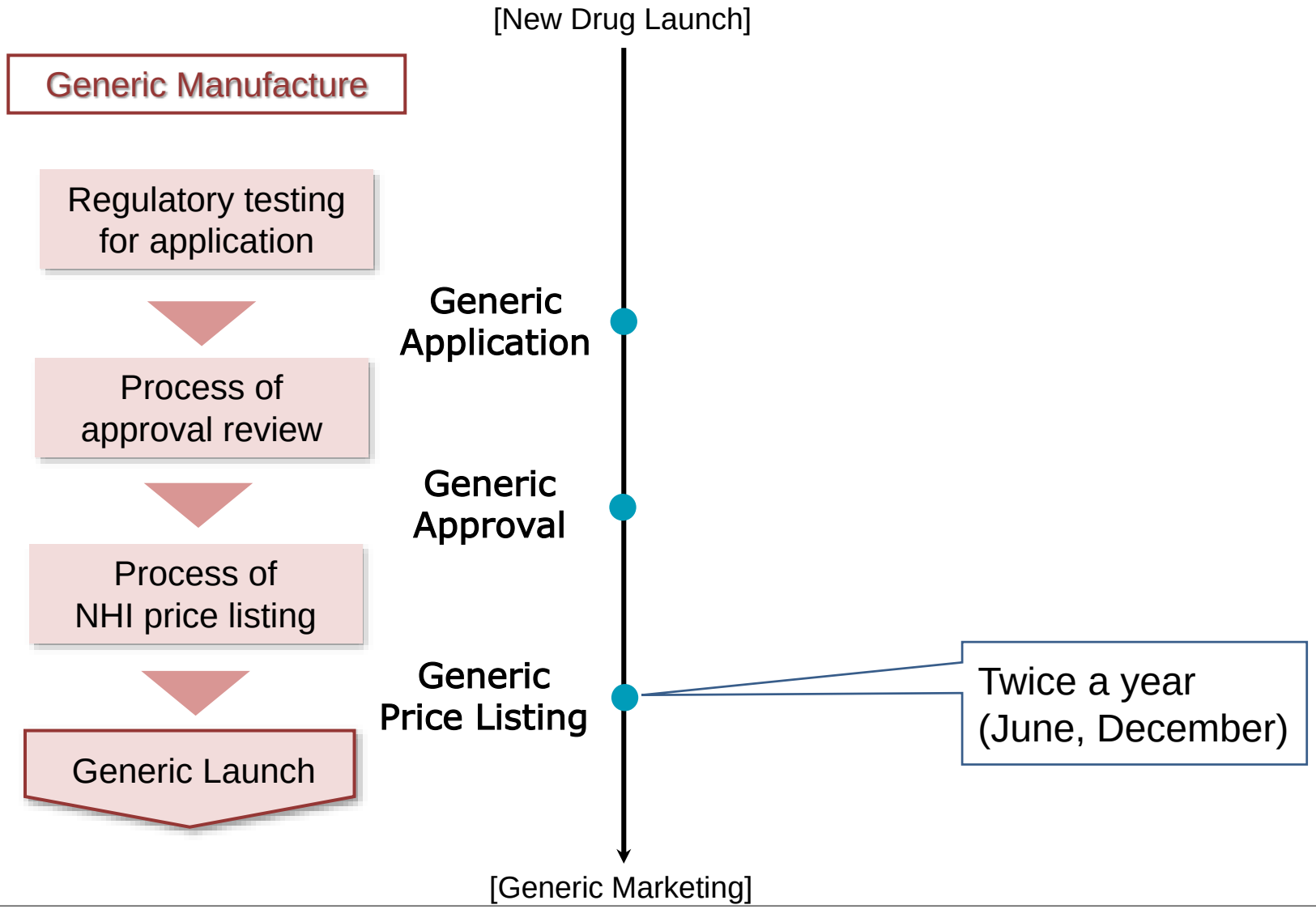
Framework of Patent Linkage in Japan

- “Patent Linkage” in Japan was introduced independently of the US system.



*1 PMDA: Pharmaceuticals and Medical Devices Agency
*2 MHLW: the Ministry of Health, Labor and Welfare
*3 FPMAJ: Federation of Pharmaceutical Manufacturers' Associations of Japan

Time Constraints for Generic Launch in Japan



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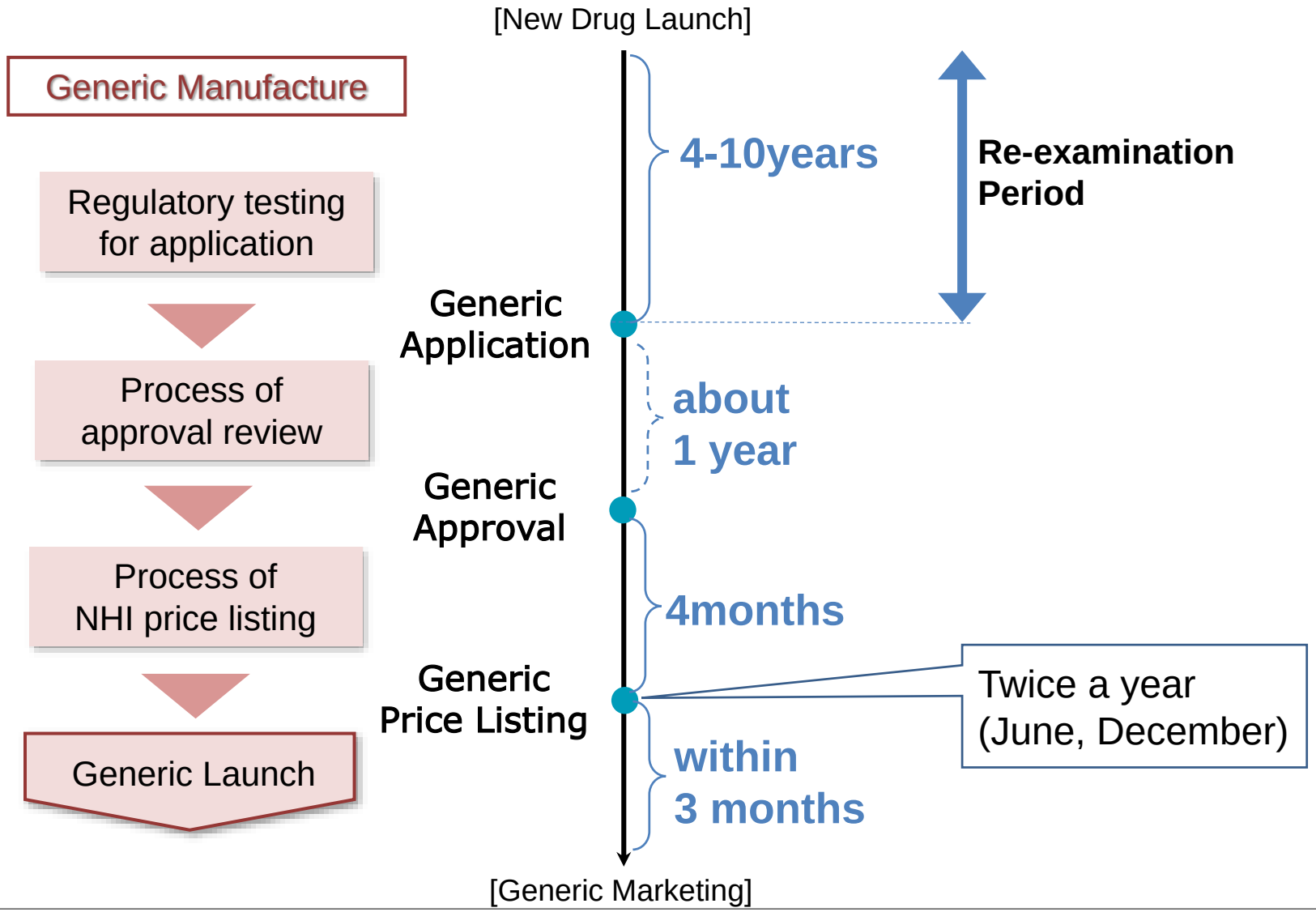
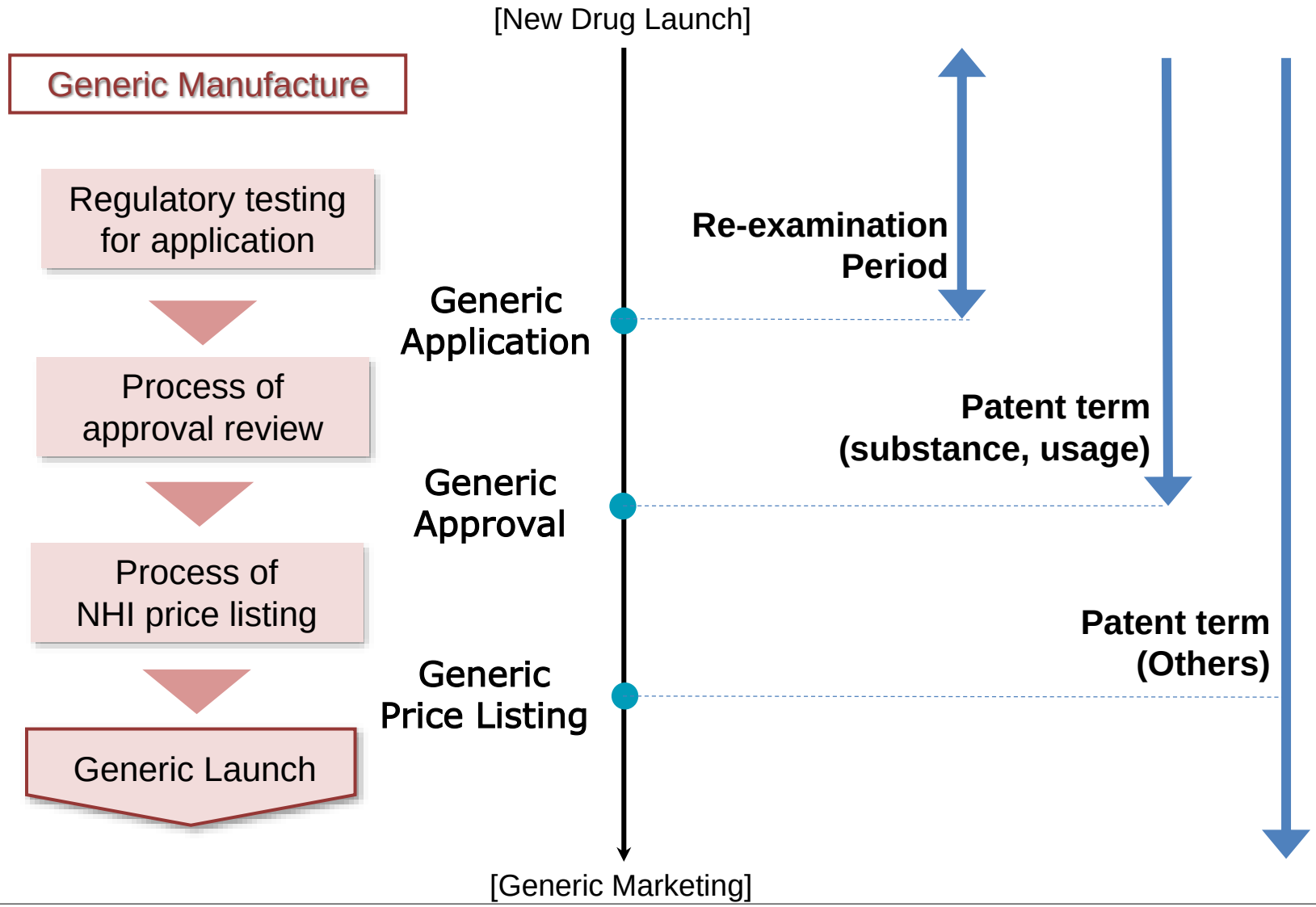


Time Constraints for Generic Launch in Japan

Control of the generic approval process under patents of a new drug



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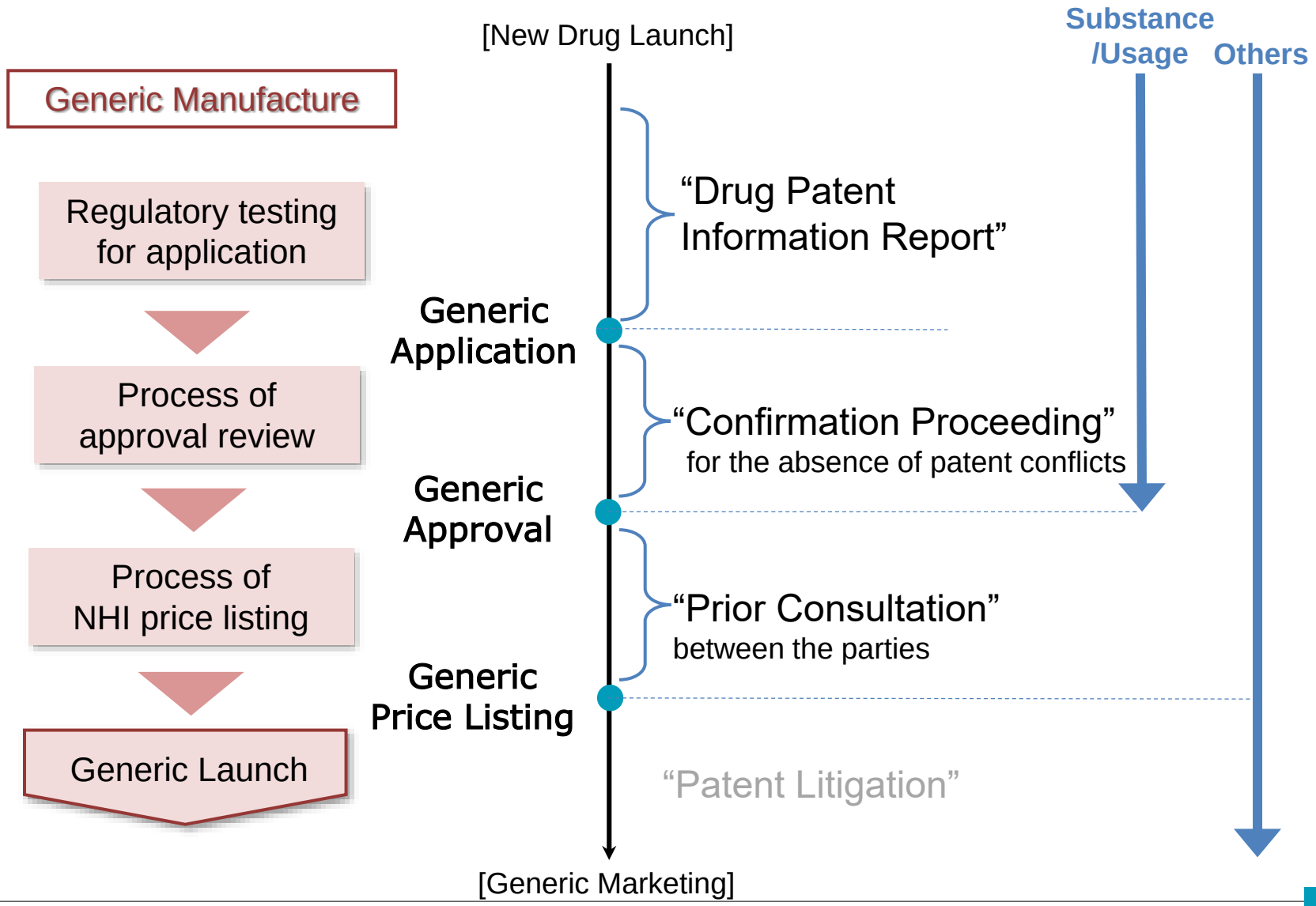

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Framework:
Features of Patent Linkage System in Japan

- No legal stipulation
  - Based on the notifications of MHLW*
  - Confirmation proceedings for “a possible stable supply after generic launch”
  - The patent office or the courts are not involved

- Reduction patent disputes after generic launch
  - The absence of substance/usage patents is checked on generic approval, while a prior consultation for other patents between the parties is requested before NHI drug price listing
  - If the prior consultation is unsuccessful, patent lawsuits could be filed after generic launch

- No incentives for early market entry of generic drug
  - No generic market exclusivity
  - No publishment of drug patent lists

*MHLW: the Ministry of Health, Labor and Welfare

Framework of Patent Linkage in Japan

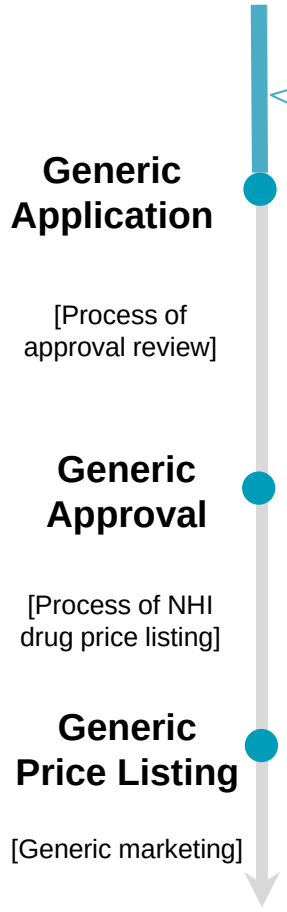
- “Patent Linkage” in Japan was introduced independently of the US system.

	Government Agency (PMDA*1/MHLW*2)	Generic Manufacturer	Brand-named Company
Generic Application [Process of approval review]	***(No publishing drug patent list)***		■ (Optional) Submit “Drug Patent Information Report Form” for PMDA
	■ Check for the absence of <u>any substance/usage patent</u> on generic approval. [Generic drug will not be approved until the confirmation]	***(No notification for the patent holder)*** ■ Proof for PMDA the generic drug can be supplied immediately after approval.	***(No request for the authorities to prevent of generic marketing)***
Generic Approval [Process of NHI drug price listing]	■ Provide the generic approval information to the public (and direct to FPMAJ*3) [Other patents are not considered on drug price listing]	■ Consult with the patent holder concerning <u>other patents</u> prior to NHI drug price listing procedure	■ Notification of generic approval by PMDA ■ Notice to the generic manufacturer if they have <u>other patents</u> suspected to be infringed
Generic Price Listing [Generic marketing]		***(No generic exclusivity)***	■ A patent lawsuit may be filed in case the prior consultation unsuccessful

*1 PMDA: Pharmaceuticals and Medical Devices Agency
*2 MHLW: the Ministry of Health, Labor and Welfare
*3 FPMAJ: Federation of Pharmaceutical Manufacturers' Associations of Japan

Framework:
"Drug Patent Information Report"

- Notification No.765 of PE/PAB(October 4, 1994)



- Brand-named companies (or patent holders) are requested to submit "Drug Patent Information Report" to PMDA before the end of the re-examination searching period.
  - However, submission is voluntary and will not be disclosed to the public.

“Drug Patent Information Report Form”

（別紙）

医薬品特許情報報告書

平成　　年　　月　　日

独立行政法人医薬品医療機器総合機構一般薬等審査部長　殿

報告者：　　㊞

住　所：
担当者名：
連絡先 TEL
FAX

成分名（一般的名称） （成分コード）	（　　）
販売名 （承認番号） （承認年月日）	 （　　） （　　年　　月　　日　　）
製造販売業者名 （業者コード） （特許との関係）	 （　　） （　　）
特許番号 （特許出願番号） （特許公開番号） （特許公告番号）	特許登録　第　　号 （特願　第　　号：　年　月　日出願） （特開　第　　号：　年　月　日公開） （特公　第　　号：　年　月　日公告）
特許登録日	年　　月　　日
特許期間満了日 （特許期間延長）	年　　月　　日 （延長期間満了日：　年　　月　　日）
特許権者名	
特許の種類	
特許と医薬品の関係	

General notes

1. A report form must be submitted for each patent.
2. If, after submission of the report form, it becomes necessary to change the contents of the report due to the progress of patent application examination, etc., the applicant should promptly submit a report form with the changed contents. (The date of submission of the report before the change and the point of change shall be noted in the notes column.)

Attachment of Notification No.765 of PE/PAB(October 4, 1994)

[Reporting party]:

- The reporter may be either the authorized holder of marketing approval including the active ingredient or the patentee (patent applicant).

[Name of Ingredient]

- Enter the generic name of the active ingredient(s) of the drug concerned.
- Ingredient codes should be listed for those submitted on or after April 1, 1995.

[Trade name]

- The marketing name, approval number and date of approval of the drug concerned should be stated accurately.

[Name of manufacturer/distributor]

- Enter the authorized holder of marketing approval for the pharmaceutical product of the marketing name.
- If the manufacturer/distributor is the patentee (patent applicant) itself, the term "patentee" or "patent applicant" should be used.
- If the manufacturer/distributor is another person, the relationship to the patent should be stated briefly, such as "exclusive licensee" or "non-exclusive licensee."

[Patent number]

- If the patent is issued, enter the patent number.
- If the patent has not yet been issued, enter the latest status at the time of submission of this report form.

[Date of patent issued]

- If the patent has been issued, enter the patent number correctly.

[Date of expiration of patent term]

- If an application for registration of patent term extension has been filed, also enter the date of expiration of the extended patent term.

[Name of patentee]

- If the patent has been issued, enter the name of the patentee. If the patent is not yet issued, enter the name of the patent applicant.
- In case of co-ownership, enter the names of all patentees (patent applicants).

[Type of patent]

- Enter whether the patent is a substance patent or a usage patent.

[Relationship between the patent and the drug product]

- Describe the relationship between the patent and the pharmaceutical product.
- E.g., A patent on a substance related to an API (active ingredient)

Framework:
"Proof of Immediate Supply after Approval"

- Notification No.765 of PE/PAB(October 4, 1994)
- Office Communication of PE/PAB(February 9, 1995)

Generic Application

[Process of approval review]

Generic Approval

[Process of NHI drug price listing]

Generic Price Listing

[Generic marketing]

- Generic manufacturers shall indicate whether or not there is a substance/usage patent on the active ingredient of the original drug in their application.
  - If there is any substance/usage patent, one of the following proofs of immediate supply after approval must be attached.

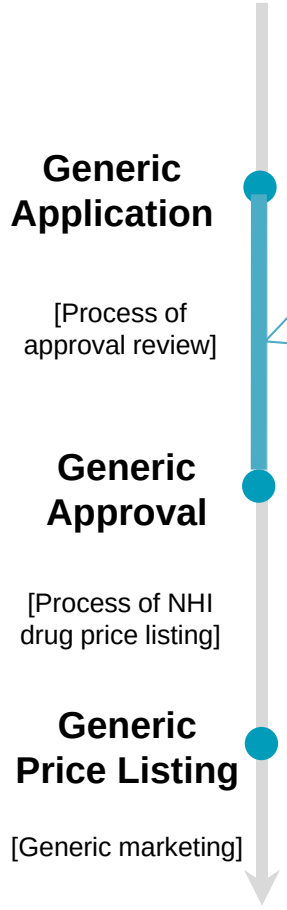
1. Proof of patent lapse
   e.g., closed patent register, patent details (patent number, name of patentee, patent term, etc.)
2. Proof of patent invalidation*
   e.g., patent invalidation trial decision, court decision
3. Proof of consent from the patentee or exclusive licensee*
   e.g., contract, agreement

*Patent details (patent number, name of the patentee, patent term, etc.) should be attached as reference material.

Office Communication of PE/PAB, dated February 9, 1995

Framework:
"Confirmation for the absence of patent conflicts"

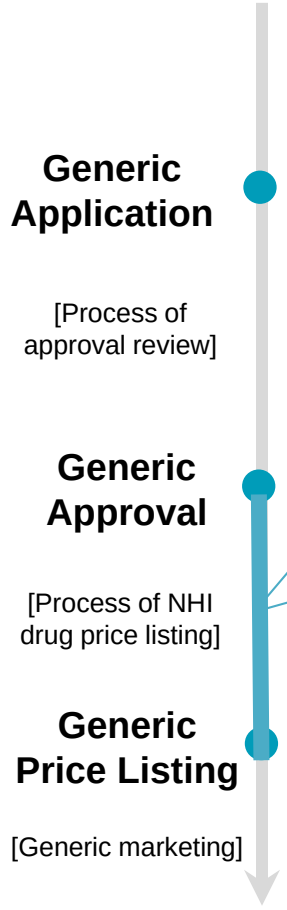
- Notification No.765 of PE/PAB(October 4, 1994)
- Office Communication of PE/PAB, dated June 28,1995
- Notification No.0605001 of EA/HPB & No.0605014 of PE/PFSB(June 5, 2009)



- PMDA/MHLW check the absence of patent conflicts between a brand-name company and the generic manufacturer during the approval review.
  - A generic drug shall not be approved, if PMDA/MHLW find the active ingredient can not be manufactured because of existing substance/usage patents on the original drug.
  - A generic drug may be partially approved, if they find the drug, under certain indications(including dosage or administration), can be manufactured despite the existence of usage patents on a different indication.

Framework:
"Prior Consultation" between the parties

- Notification No.0115001 of EA/HPB(January 15, 2009)
- Notification No.0605001 of EA/HPB & No.0605014 of PE/PFSB(June 5, 2009)



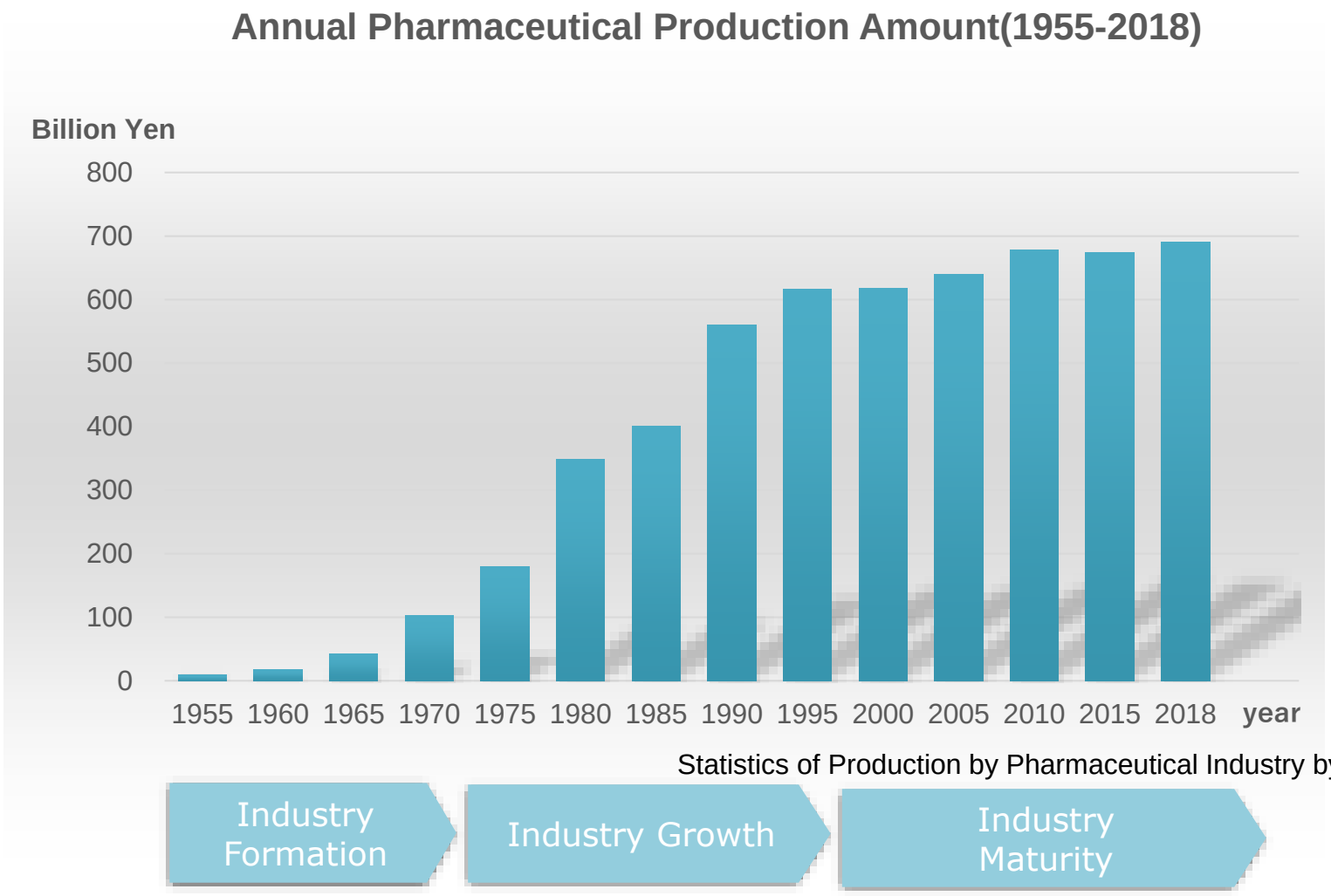
- Generic manufacturers shall apply only for the item which is expected to ensure a stable supply in the NHI drug price listing procedure
  - If there will be any concerns of a stable supply because of patents, a prior consultation with the brand-named company(patent holders) should be made.
  - In order to confirm that a stable supply of the generic drug is ensured, objective evidence such as a written consent from the patent holders may be requested as necessary.

Framework:
"Prior Consultation" between the parties

- Notification No.0115001 of EA/HPB(January 15, 2009)
- Notification No.0605001 of EA/HPB & No.0605014 of PE/PFSB(June 5, 2009)

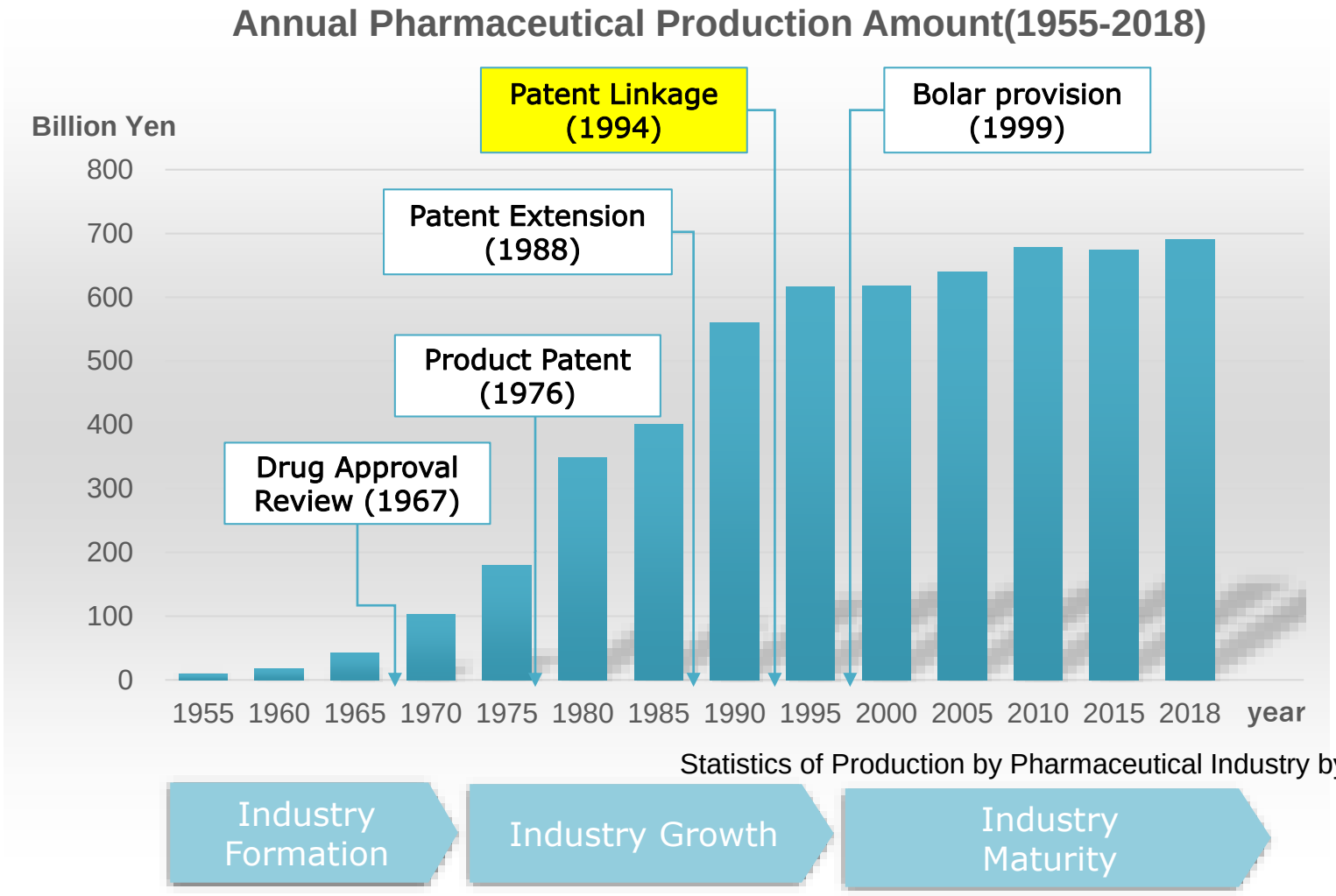
- In practice, the generic approval information is provided timely and directly from MHLW to FPMA.
  - Patent holders notify the generic manufacturer if they have patents other than substance/usage patents(e.g., process, formulation, etc.) suspected to be infringed
- Even if prior consultation is unsuccessful, the generic drug can be listed on the NHI drug price list.
  - Some generic manufactures launch their products in a risk of a patent lawsuit, while others postpone listing the generic drug on the NHI drug price list.
  - There are few cases or patent lawsuits being filed.

History:
Industry Development and IP Protections in Japan



Statistics of Production by Pharmaceutical Industry by MHLW.

History:
Industry Development and IP Protections in Japan



Statistics of Production by Pharmaceutical Industry by MHLW.

History:
Introduction of Patent Linkage System in 1994

- Rapid increase in the number of patent lawsuits filed after the launch of generics
  - **29** cases (1983-1987) ⇒ **218** cases (1988-1992)

- *"Report of Advisory Committee on the Future Vision of Pharmaceuticals in the 21st Century"*, Pharmaceutical Affairs Bureau, MHLW in 1993
  - Recommendation of conditions to be considered by the government for the generic drug promotion;
    1. Ensuring for a stable supply of generic drugs
    2. A system for collecting and providing generic drug information
    3. Thorough manufacturing and quality control
    4. Consideration of patent information on the generic approval review process
    5. The NHI drug price calculation method

History:
Relevant Notifications of MHLW

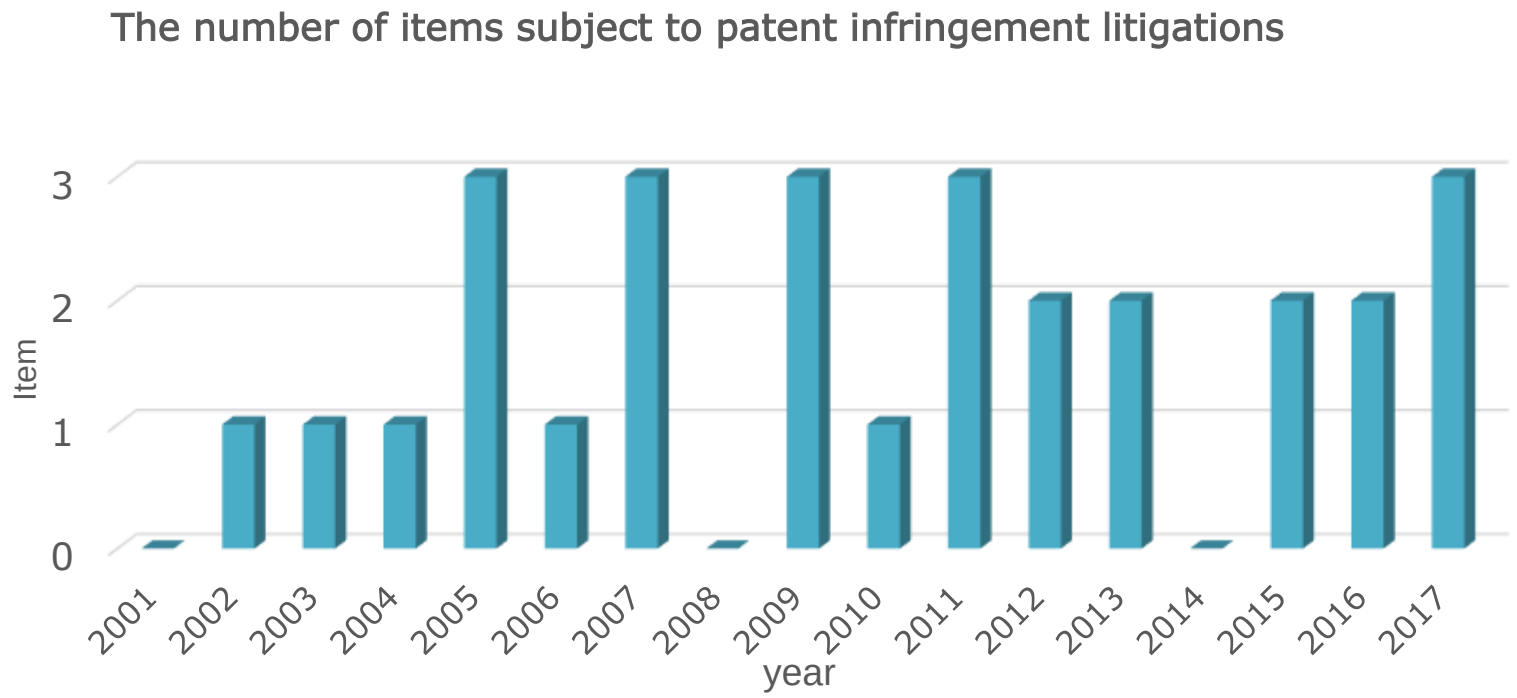
Date	Title	Type	Division	No.
October 4, 1994	Handling of Drug Patent Information for Approval Review	Notification of the Director	Pharmaceutical Evaluation(PE) Division, Pharmaceutical Affairs Bureau(PAB)	Notification No.765 of PE/PAB
February 9, 1995	Patent information to be attached to the application for approval of drug manufacture (import)	Office Communication	PE Division, PAB	—
June 28, 1995	Patent Term and the Timing of Generic Drug Application	Office Communication	Pharmaceutical Evaluation Division, PAB	—
January 15, 2009	Listing Generic Drugs on NHI Drug Price List	Notification of the Director	Economic Affairs(EA) Division, Health Policy Bureau(HPB)	Notification No.0115001 of EA/HPB
June 5, 2009	Handling of Drug Patents in the process of generic approval reviews and of the listing on NHI Drug Price List under the Pharmaceutical Affairs Law	Notification of the Directors	EA Division, HPB PE Division, Pharmaceutical and Food Safety Bureau(PFSB)	Notification No.0605001 of EA/HPB Notification No.0605014 of PE/PFSB

"In order to prevent patent disputes after approval from the viewpoint of ensuring a stable supply of pharmaceutical products, measures such as checking for patent conflicts between the generic product and the brand name product during the approval review of the generic product should be taken."

Report of Advisory Committee on the Future Vision of Pharmaceuticals in the 21st Century

Impacts:
Recent Trends in Patent lawsuits after Generic Launch

- **0-3 items** subject to patent lawsuits per year
  - *cf. 29 cases (1983-1987) ⇒ 218 cases (1988-1992)*

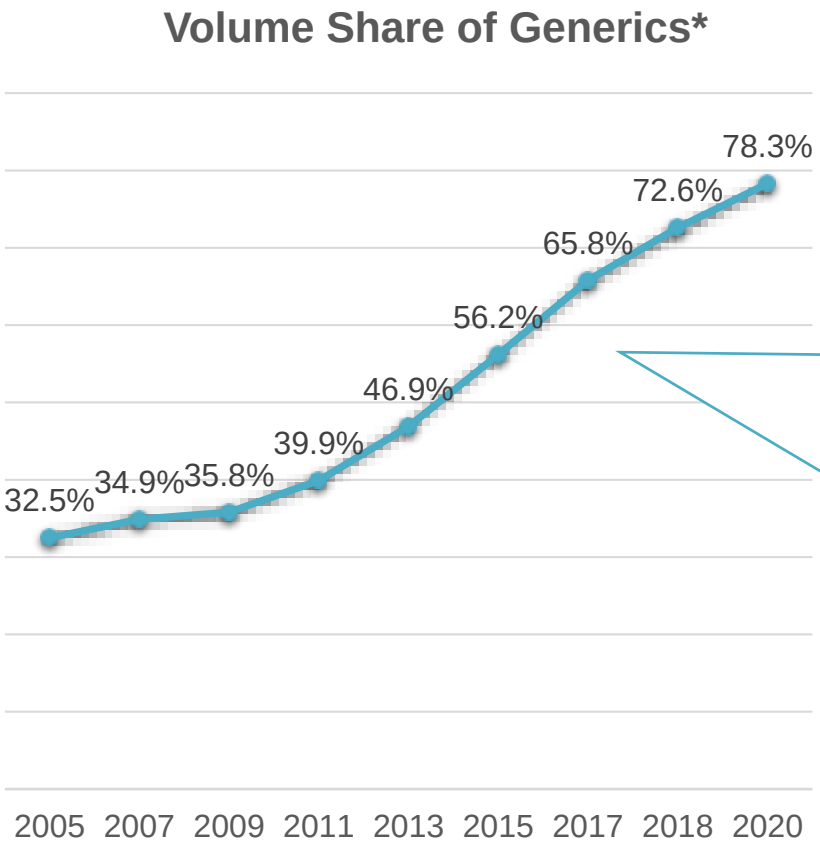


Examples of patent infringement cases from 2000 to 2017 (as of Aug 2018)

Masuda S, Journal of Generic Medicines, vol.15(1), 10-17, 2019 (revised in part)

Year	Original product name (Generic name)	Type of Patent	Days	Result
2002	GASTER®(Famotidine)	Substance(Crystal), Process	977	Non-infringement (High Court)
2003	LIVACT® (Amino acids)	Formulation, Process	538	Infringement (District Court)
2004	MEVALOTIN®(Pravastatin)	Formulation (stabilization)	207	Settlement (District Court)
2005	OMEPRAL®(Omeprazole)	Formulation	323	Settlement (District Court)
2005	CEFZON® capsule (Cefdinir)	Substance(Crystal)	902	Infringement (High Court)
2005	HARNAL® capsule (Tamsulosin)	Formulation	328	Settlement (District Court)
2006	NEORAL® (Cyclosporine)	Formulation	648	Settlement (District Court)
2007	GLUCOBAY® (Acarbose)	Composition	720	Settlement (High Court)
2007	KREMEZIN® (Spherical adsorption coal)	Formulation	1890	Settlement (High Court)
2009	CRAVIT® (Levofloxacin)	Substance(Cristal), Usage	219	Non-infringement (High Court)
2009	MUCOSTA® (Rebamipide)	Usage	154	Withdrawal
2009	FLOMOX® (Cefcapene Pivoxil)	Substance(Crystal)	428	Settlement (District Court)
2010	EBASTEL® (Ebastine)	Formulation	529	Non-infringement (District Court)
2011	ACTOS® (Pioglitazone)	Combination	624	Non-infringement (District Court)
2012	LIPITOR® (Atorvastatin)	Substance(Crystal)	603	Invalid (High Court)
2012	ALLEGRA® (Fexofenadine)	Usage	518	Settlement (District Court)
2013	OXAROL® (Maxacalcitol)	Process	1494	Infringement (Supreme Court)
2013	LIVALO® (Pitavastatin)	Substance(Crystal), Formulation	805	Non-infringement (High Court)
2015	EVISTA® (Raloxifene)	Usage	380	Invalid (High Court)
2016	OZEX® (Tosufloxacin)	Formulation	380	Settlement (District Court)
2016	ELPLAT® (Oxaliplatin)	Formulation	722	Non-infringement (High Court)
2017	HERCEPTIN® (Trastuzumab)	Usage & dose	237	Abandonment (District Court)
2017	ZYVOX® (Linezolid)	Usage	Unknown	Settlement (District Court)
2017	RITUXAN® (Rituximab)	Usage	-	Pending (District Court)

Impacts:
Future Challenges in the Era of "80% Generic Use Rate"



Initiatives for "80% Generic Use Rate" in 2020

- Unification of generic drug names (2005)
  - Generic name + dosage form + content + company name (trade name)
- Revision of prescription forms (2006-)
  - "Changeable" with signature(2006)
  - "Unchangeable" with signature(2008)
  - Select "Changeable/Unchangeable" for each prescription drug(2012)
- Additional fee for generic dispensing (2008-)
  - Pharmacy with more than 55% generics(2008)
  - with more than 65% generics(2012)
  - with more than 80-90% generics(2022)

$$* \frac{\text{[Volume of Generic Drugs].}}{\text{[Volume of Original Drug (patent expired)] + [Volume of Generic Drugs].}}$$

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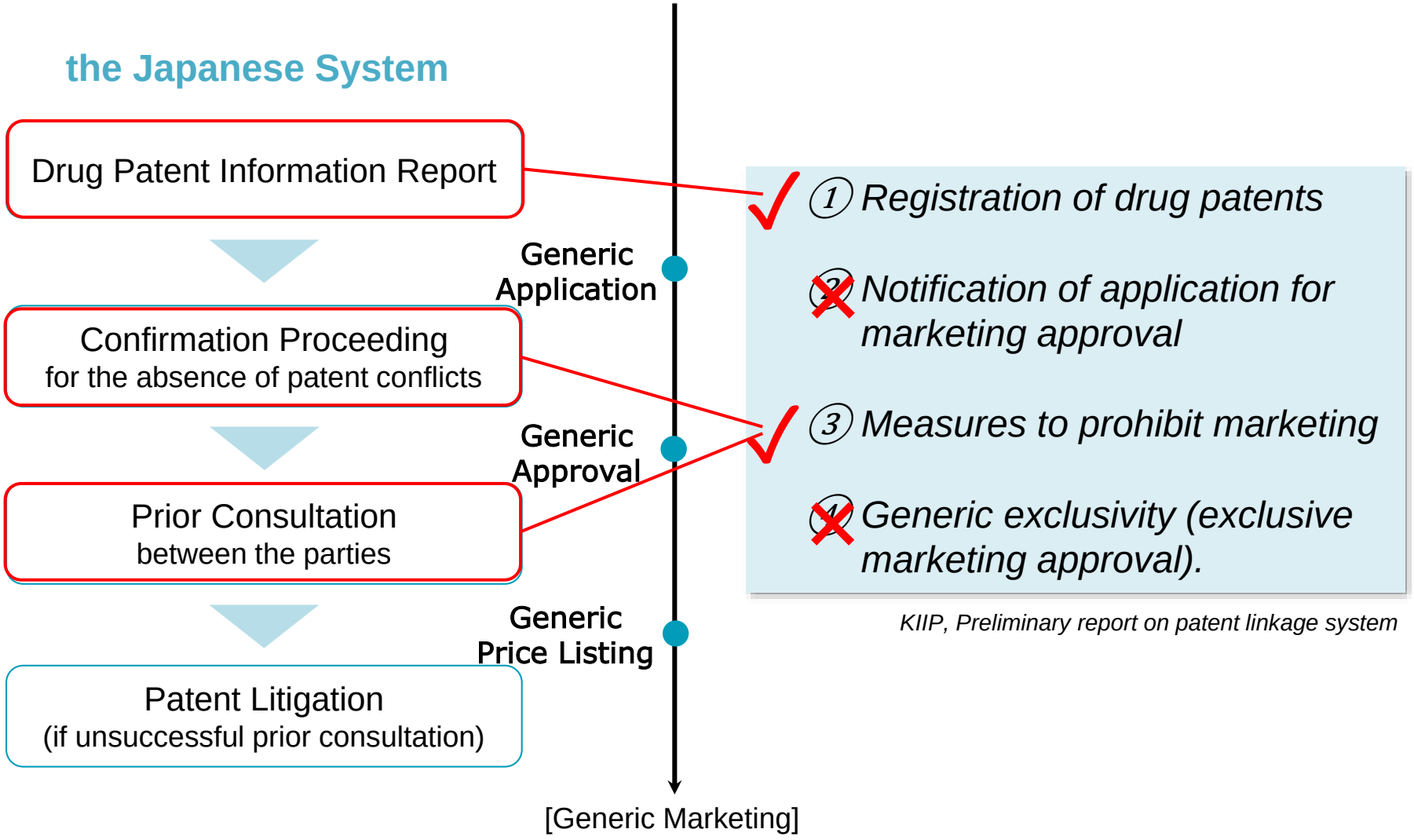
Is the Japanese System "Patent Linkage" ?
Key Components of the Patent Linkage System



KIIP, Preliminary report on patent linkage system

Is the Japanese System "Patent Linkage" ?
CPTPP Agreement

Article 18.53: Measures Relating to the Marketing of Certain Pharmaceutical Products

1. If a Party permits, as a condition of approving the marketing of a pharmaceutical product, persons, other than the person originally submitting the safety and efficacy information, to rely on evidence or information concerning the safety and efficacy of a product that was previously approved, such as evidence of prior marketing approval by the Party or in another territory, that Party shall provide:
   (a) a system to provide notice to a patent holder[62] or to allow for a patent holder to be notified prior to the marketing of such a pharmaceutical product, that such other person is seeking to market that product during the term of an applicable patent claiming the approved product or its approved method of use;
   (b) adequate time and opportunity for such a patent holder to seek, prior to the marketing of an allegedly infringing product[63], available remedies in subparagraph (c); and
   (c) procedures, such as judicial or administrative proceedings, and expeditious remedies, such as preliminary injunctions or equivalent effective provisional measures, for the timely resolution of disputes concerning the validity or infringement of an applicable patent claiming an approved pharmaceutical product or its approved method of use.

2. As an alternative to paragraph 1, a Party shall instead adopt or maintain a system other than judicial proceedings that precludes, based upon patent-related information submitted to the marketing approval authority by a patent holder or the applicant for marketing approval, or based on direct coordination between the marketing approval authority and the patent office, the issuance of marketing approval to any third person seeking to market a pharmaceutical product subject to a patent claiming that product, unless by consent or acquiescence of the patent holder.

62 For greater certainty, for the purposes of this Article, a Party may provide that a "patent holder" includes a patent licensee or the authorised holder of marketing approval.
63 For the purposes of paragraph 1(b), a Party may treat "marketing" as commencing at the time of listing for purposes of the reimbursement of pharmaceutical products pursuant to a healthcare programme operated by a Party and inscribed in the Appendix to Annex 26-A (Transparency and Procedural Fairness for Pharmaceutical Products and Medical Devices).

Is the Japanese System "Patent Linkage" ?
CPTPP Agreement

the Japanese System

Drug Patent Information Report

Generic Application

Confirmation Proceeding
for the absence of patent conflicts

Generic Approval

Prior Consultation
between the parties

Generic Price Listing

Patent Litigation
(if unsuccessful prior consultation)

[Generic Marketing]

＜Article 18.53.1＞

a. prior to the marketing of generics;
   - **A system of notice** for a patent holder that a generic manufacturer is seeking to market the product covered by patents during their terms

b. prior to the marketing of an allegedly infringing generics [note];
   - **Adequate time and opportunity for such a patent holder to seek available remedies in (c)**

c. for the timely resolution of disputes concerning the validity or infringement of an applicable patent:
   - **Procedures**(such as judicial or administrative proceedings)
   - **Expeditious remedies**(such as preliminary injunctions or equivalent effective provisional measures)

＜Article 18.53.2＞

Based upon patent-related information from patent holders etc. or direct from patent office;
   - **A system other than judicial proceedings** that precludes the issuance of generic marketing approval, unless by consent or acquiescence of the patent holder.

note: a Party may treat "marketing" as commencing at the time of listing for purposes of the reimbursement of pharmaceutical products pursuant to a healthcare programme

CPTPP	Japan
＜Article 18.53.1＞ a. prior to the marketing of generics; - **A system of notice** for a patent holder that a generic manufacturer is seeking to market the product covered by patents during their terms b. prior to the marketing of an allegedly infringing generics; - **Adequate time and opportunity for such a patent holder to seek available remedies in (c)** c. for the timely resolution of disputes concerning the validity or infringement of an applicable patent: - **Procedures**(such as judicial or administrative proceedings) - **Expeditious remedies**(such as preliminary injunctions or equivalent effective provisional measures)	■ In practice, the generic approval information is provided timely and directly from MHLW to the Federation of Pharmaceutical Manufacturers' Association of Japan (FPMAJ) http://www.fpmaj.gr.jp/iyaku/index.htm ■ "Prior Consultation" with patent holders should be taken, if any concerns of a stable supply because of patents ■ A patent lawsuit may be filed in case the prior consultation unsuccessful
＜Article 18.53.2＞ Based upon patent-related information from patent holders etc. or direct from patent office; - **A system other than judicial proceedings** that precludes the issuance of generic marketing approval, unless by consent or acquiescence of the patent holder.	■ "Drug Patent Information Report Form" for PMDA ■ Confirmation proceedings for the absence of any product or usage patent at the timing of generic approval

Conclusion

- Patent Linkage System in Japan is unique by its own and not influenced by the US system.
  - From the viewpoint of ensuring a stable generics supply:
    - The system aims to reduce patent disputes after the launch.
    - It serves as an administrative guidance by the MHLW.
  - The system is generally accepted by both brand-named companies and generic manufacturers.

- Future challenges to the system:
  - The increase in patent disputes because of a change in the balance of the markets
  - Conformity and standardization to international rules