Current Situation of Generic Drugs Assessment, and Expectation in Japan.

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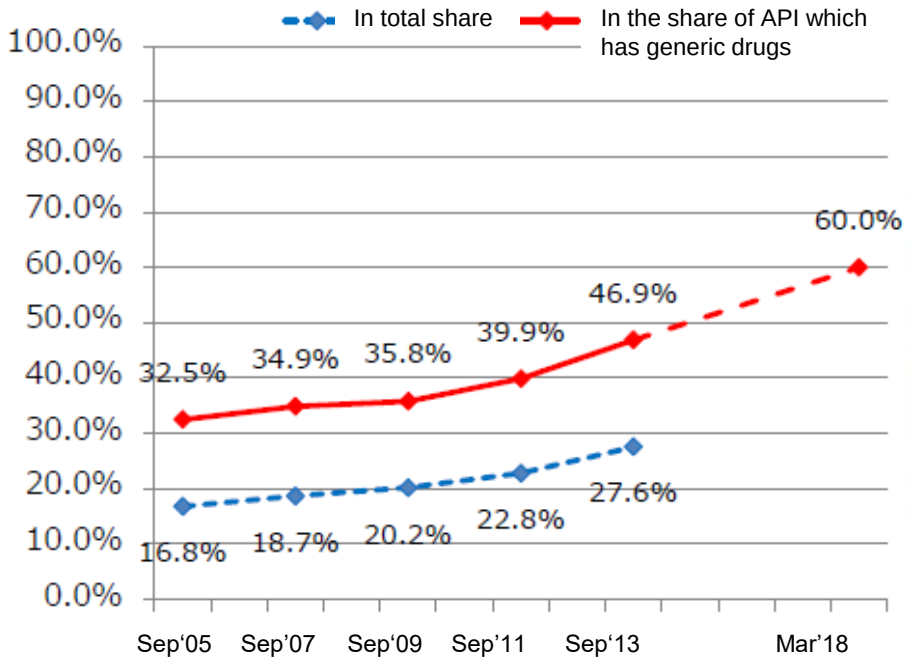
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

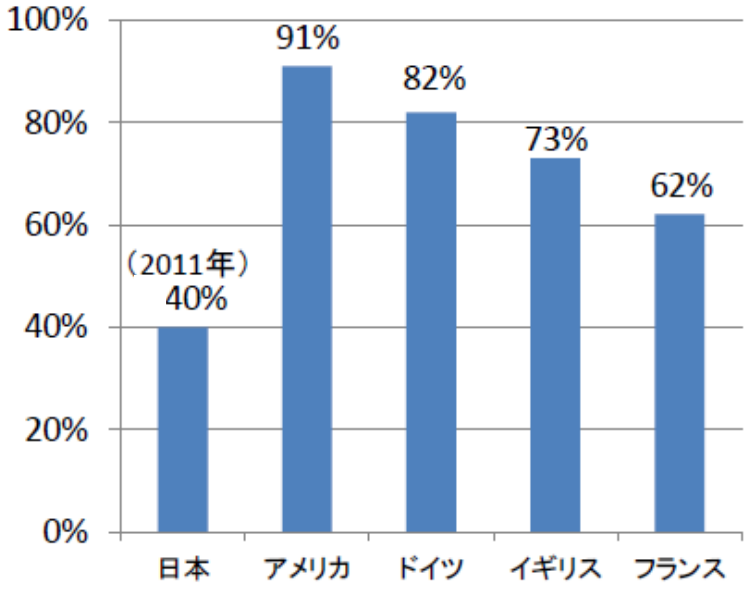
Market Share of Generic Drugs

Trends in the Market Share of Generic Drugs Japan



Source: MHLW webpage

Comparison of the Market Share of Generic Drugs



Supply Chain Information (chemical DS)

Status of procurement of generic API listed in the health insurance price list (FY2011)

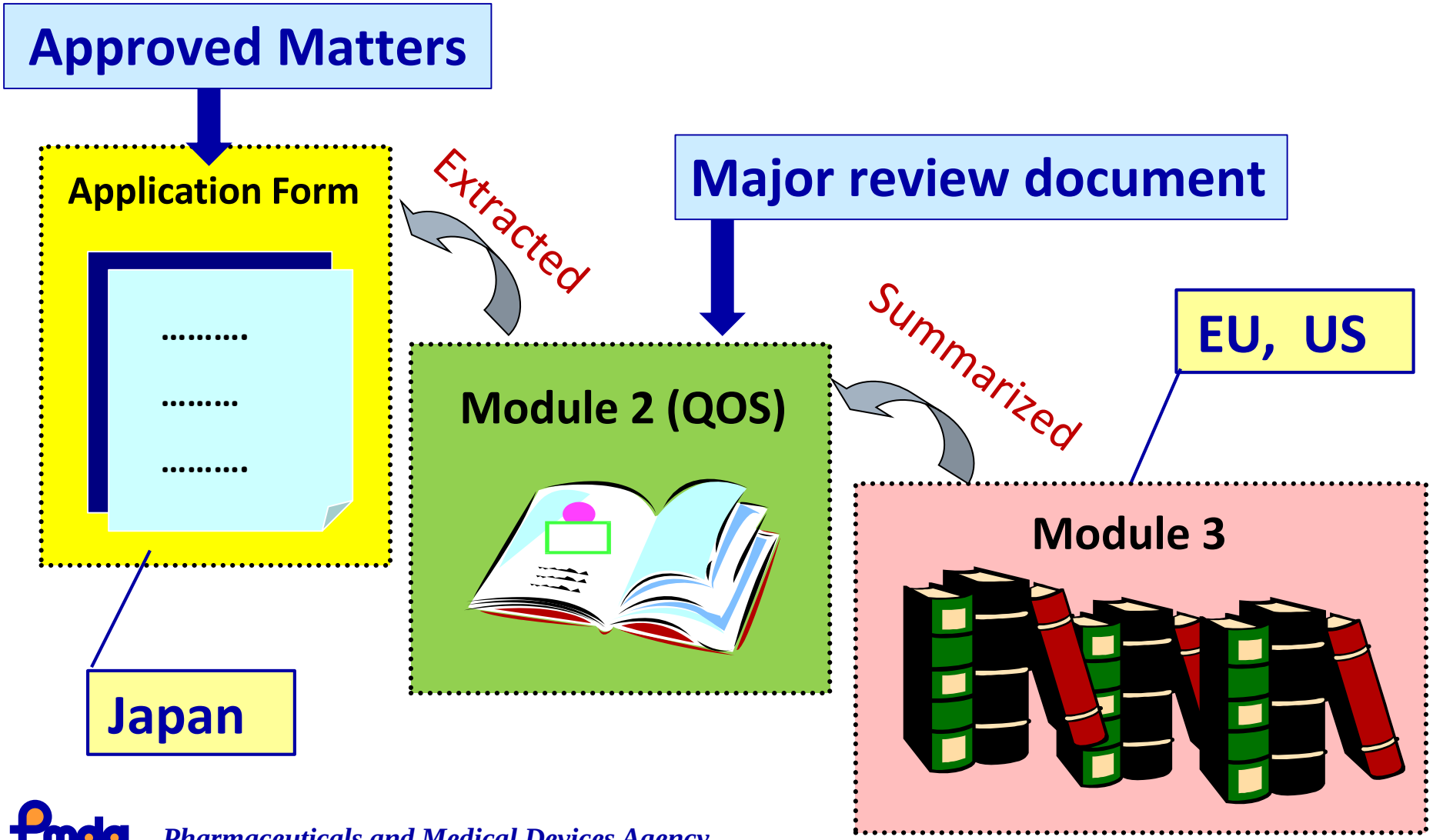
	Price (at the time of shipment) (million yen)		Number of items	
		Composition percentage		Composition percentage
Items using the drug substance for which all the processes involved in its manufacturing are carried out in Japan	195,251	30.9%	2,896	37.5%
Items using drug substances for which the intermediate product is imported and some reaction processes are carried out in Japan	36,443	5.8%	538	7.0%
Items for which crude or final product is imported and purification or processing is carried out in Japan	51,753	8.2%	586	7.6%
Items which use the imported drug substance as it is	288,888	45.8%	3,672	47.5%

Prepared based on the investigation and review report (March 2013) on evaluation criteria etc., for improving the reliability of generic drugs in FY2012

Today's Contents

- Application Form (AF), found in Module 1.2, is a legally binding document in Japan.
- A post-approval regulatory action is required if a marketing authorization holder changes the description in the AF (included DMF).
- AF provides the transparency and flexibility in terms of post-approval changes.
- In change control of the approval certificate, the API development strategy must be thoroughly explained using CTD at the time of application

Relationship between Application Form and CTD Documents in Japan



Change of generic drug approval application data to CTD format

- "Handling of documents to be attached with the prescription drugs approval application"

(Notification No. 0311-3 of the Evaluation and Licensing Division, PSEHB dated March 11, 2016)

- Application target

Among the prescription drugs given in Appendix 2-(1) of PSEHB notification, it corresponds to the drugs that fall under the classification of (8-2) drugs in an additional dosage form (those drugs that are not in the re-examination period), and (10-3) other drugs (those drugs that are no in the re-examination period).

- Basic concept

In principle, the documents to be attached with the approval application shall be compiled in accordance with the CTD

- Effective date

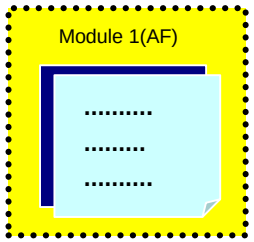
CTD application from March 1, 2018 onward

- Checking of required items using the attached checklist

Matters to be described in Mfg. process section

All processes from raw material(s) to packaging process

- A flow diagram of manufacturing process including:
  - Raw materials
  - Charge-in amount
  - Yield
  - Solvent
  - Intermediate materials
  - Process parameter (e.g. Target Value/Set Value)



- A narrative description of manufacturing process
  - Acceptance criteria of starting material(s) and intermediate materials
  - In process control, Design Space and RTRT etc.

Description of Partial & Minor Change Matters in AF

- Enter items other than target/set values in
  - Nothing: Partial Change Matter
  - “　　”: Minor Change Matter
- Enter target/set values of process parameters and standard charge-in amounts in
  - 《　　》: Partial Change Matter
  - 『　　』: Minor Change Matter

Step 1 (Critical Step)

CP-6『(230kg)』, tetrahydrofuran『(1300L)』, sodium carbonate『(42.4kg)』 are combined. Ethyl chloroformate “158～592kg” is added and the mixture is heated at temperature up to reflux. ・・・・

Water (“25 to 35%” *weight per weight of ethanol) is added and the mixture is stirred at 『20℃』.

Acknowledgement : Sakuramil (Sakuramil S2 mock)
http://www.nihs.go.jp/drug/section3/H23SakuramillMock(Eng).pdf

AF system in Japan provides a clear description of post approval change controls.

- Transparency
  - We can clearly share the regulatory commitments between applicants and regulators .
  - Module 2 can be a good communication document because Module 2 is just a review document and applicants can write their narrative on Quality Overall Summary freely.
- Efficiency
  - Quality Overall Summary can facilitate our assessment because of the primary review document in Japan.

Post-Approval Change Reporting Categories

Impact on quality	Japan	US	EU
High	**Partial change Application** (approval of variation)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	**Minor change Notification** (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**SOP** (Under GMP change control)	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

Points to be noted in change control of approval certificate

- **In the drug product application, objects pertaining to minor change notification and application for approval for partial changes must be mentioned separately**

1. **The possible impact of each description item such as manufacturing process on quality of the dosage form shall be predicted**

(As per PFSB/ELD Notification No.0210001 dated February 10, 2005)

2. **Risk assessment based on item characteristics**

In case of changes, development strategies must be explained at the time of application by using CTD and checklist, for the review to be smooth.

Points to be noted at the time of application

- API
  - Quality characteristics of the API is an essential information for explaining the propriety of the dosage form design and the dosage form manufacturing process
  - MF registrant shall properly share information on quality characteristics of the API with the pharmaceutical product manufacturing and marketing approval applicant (Consistency of the drug substance and dosage form)

  Example
    - Solubility
    - Polymorphic form
    - Particle size
    - Related substances and impurities
    - Stability (impact of light, humidity and heat)
    - Equivalency of drug substances from different manufacturing plants

Points to be noted when creating documents for application (1)

- Reviewers would efficiently understanding the adequacy of the described contents

Sample 1: Details of the minor notification

No.	Process	Application (form)	Drug product standard code etc.	Demonstrated tolerance	Reason and basis for designation in the application
		Details of minor change notification	Control range	About the non-conformance boundary if it has been identified	
001	Step	『20°C』 or 『20 to 25°C』	○ to ○°C	○ to ○°C	

Sample 2: Major manufacturing parameters not described in the application (form)

No.	Process	Application (form)	Drug product standard code etc.	Demonstrated tolerance	Reason and basis for designation in the application
		Manufacturing process without the description of parameters in the application (form)	Control range	About the non-conformance boundary if it has been identified	
001	Step	Blend A “x kg” and B “x kg” by depositing in the fluid bed granulator.	○rpm ○ to ○ minutes	○ to ○rpm ○ to ○ minutes	

About the CTD format related to the application intended to reduce the total review time of new drugs (Administrative notice dated January 17, 2011)

Points to be noted when creating documents for application (2)

- **API (starting material and material control)**
  - Describe from the pertinent starting material and as a rule, describe the reaction process in terms of multiple processes
  - Note that the adequacy of manufacturing process shall not be judged only by the sufficiency of the number of reaction processes.
    → Propriety of selection of the starting material (*Rf)* ICH Q11)
    → Evaluation of the control strategy
  - Requirements of CTD and checklist
    - Was the propriety of the reaction process explained?
    - In the drug substance manufacturing process, were the control standards for raw material, critical intermediate and final intermediate to form the starting material and basic structure established or confirmed?
    - Were the control points and control values established or confirmed for all the raw materials used in the process after the final intermediate?

Problem cases related to the API manufacturing process

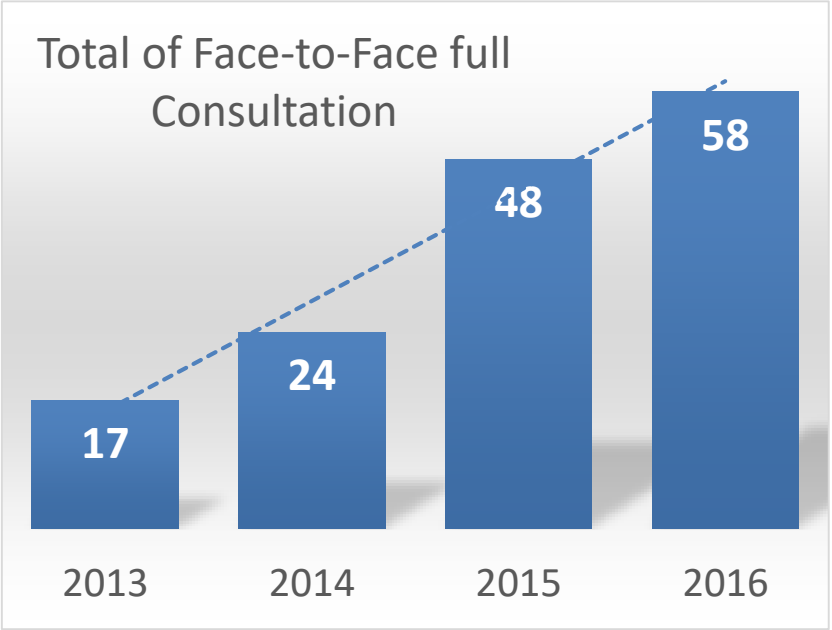
- Establishment of the drug product listed in the EP monograph as the starting material
- Change of testing method of critical raw material control points
- Major manufacturing scale was changed with no information sharing
- Change validation was not conducted for the changes in manufacturing process

etc…

Consultation Service for Quality

- Face-to-Face full Consultation

Starting in January 2012 to give guidance and advice of application materials before the submission.



- Abbreviated consultations

e.g.)Consultation on MF registration or change

- Trial Consultation

（For Partial change application, consultation to confirm whether you correspond to minor change notification)

Third Mid-term Plan（FY 2014-2018）

- Enhancement of reviewer team
  - The office of generic drugs was established in Nov 2014.
  - The number of reviewers is to be increased.
- Promotion of streamlining / Establishment of transparent review
  - Recommend of CTD application.
  - Make a review report.
  - Make use of experience in face-to-face consultation to compile product-specific BE guidances etc.
- Enhancement of consultation service
  - All applications for consultation have been accepted since Nov 2014.
  - New category of consultation is under trial.

Current policies, practices and available relevant documents for DS

- PFSB/ELD Notification No.021001 Feb 10,2005 referring to filing of DS manufacture, which recommends for applicants not to register a simple step.

- ICH Q11: Development and Manufacture of Drug Substances, Jul 10,2014
  - Implementation of Q11 in Japan has made SM selection more risk-based and applicants have submitted a longer manufacture route.

- MHLW-sponsored studies “Research of development and manufacturing information of drug substances”, Sakuramil S2 mock

Thank you for your attention !

http://www.pmda.go.jp/

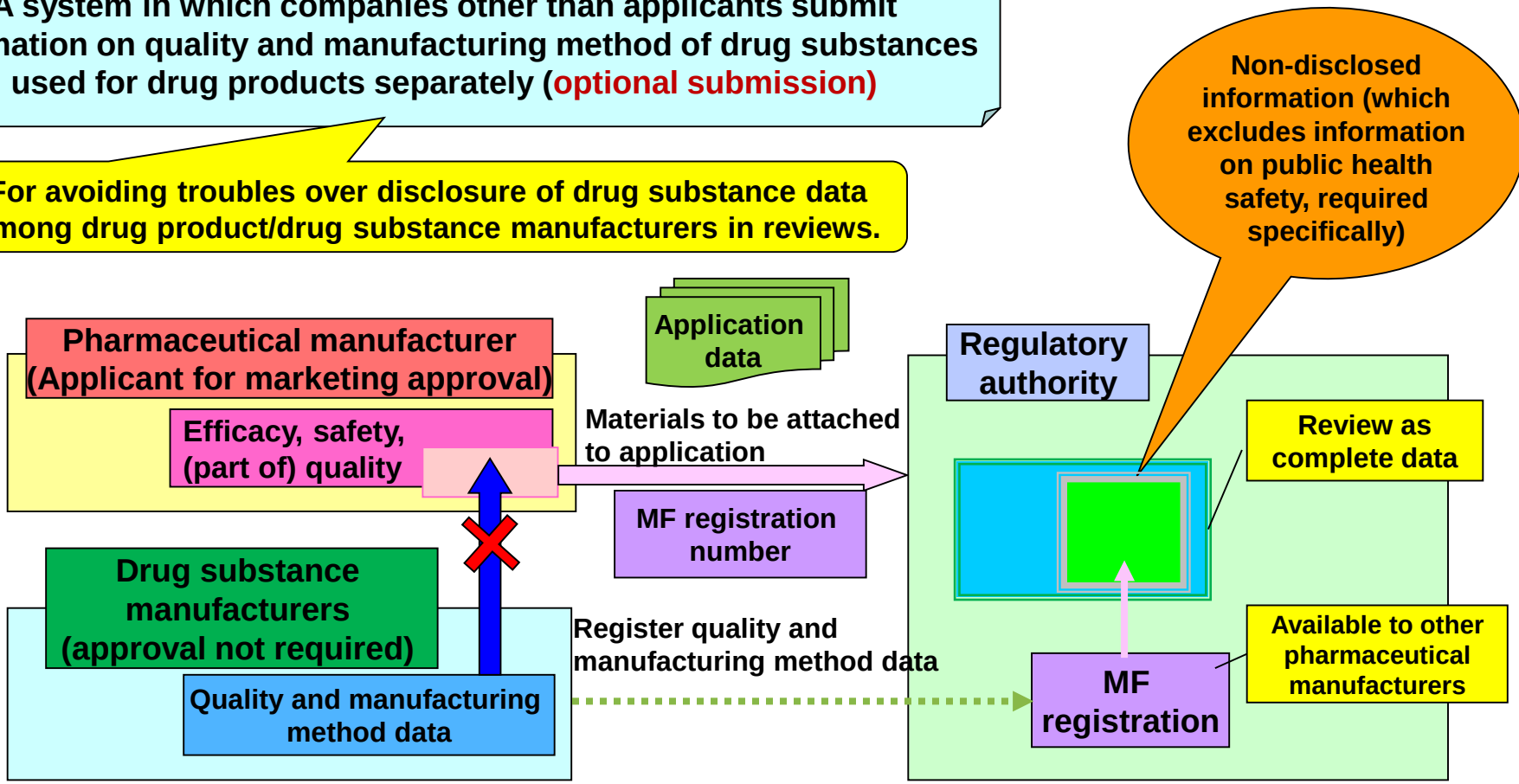
Back-up

Approval reviews for drug products quoting MF

Master file is used both in US and EU

A system in which companies other than applicants submit information on quality and manufacturing method of drug substances used for drug products separately (optional submission)

For avoiding troubles over disclosure of drug substance data among drug product/drug substance manufacturers in reviews.



Positioning of MF registration matters

- **Information registered in MF**
  - **If there are Partial documents for marketing approval application for a drugproduct**
  - **If there are Partial attached documents for marketing approval applicationfor a drug product during the drug product marketing application**
- **The registration matters shall be reviewed during approval review of drug product using the corresponding MF. In the review related to the drug product (dosage form), it is recommended to submit documents corresponding to Module 2 (outline of submitted data) of CTD apart from the Module 3.**
- **From March 1, 2017 onward, review would be conducted based on the CTD in principle for the approval application of drug product in which the corresponding MF has been cited. (Notification No. 0311-3 of the Evaluation and Licensing Division, PSEHB dated March 11, 2016)**

Concept for the description of the manufacturing process in the approval certificate

- Also refer to "Question and Answer (Q&A) on Description of Manufacturing Method in Application Forms for Drugs" (Administrative Notice from ELD, PMSB, MHLW, dated May 20, 2008), for the concept for the description of the manufacturing process.

- Concept related to relevance of details of minor change notification/details of application for approval for partial changes
  - Each firm must make appropriate decisions based on the following notifications, etc. However, the services of a consulting organization can be used if it is difficult to decide.
  - "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc., under the Revised Pharmaceutical Affairs Law" (PFSB/ELD Notification No. 0210001, February 10, 2005)

  - Other related notifications and administrative notices (Q&A)

- Administrative Notice from ELD, PMSB, MHLW, dated November 16, 2006
- Administrative Notice from ELD, PMSB, MHLW, dated December 14, 2006
- PFSB/ELD Notification No. 0112001 dated January 12, 2007
- Administrative Notice from ELD, PMSB, MHLW, dated June 28, 2010
- Administrative Notice from ELD, PMSB, MHLW, dated July 26, 2010
- PFSB/ELD Notification No. 0530-8 dated May 30, 2014
- PFSB/ELD Notification No. 0710-9 dated July 10, 2014

Supplier of the DS (Generic Drugs)

Supplier-wise status when using the imported drug substance as it is (FY2011)

	Number of firms		Amount of purchase (10,000 yen)		Number of active ingredients	
		Composition percentage		Composition percentage		Composition percentage
Total	1539		6,635,569		1893	
USA	57	3.7%	243,793	3.7%	64	3.4%
Mexico	18	1.2%	17,773	0.3%	23	1.2%
France	54	3.5%	97,469	1.5%	80	4.2%
Switzerland	43	2.8%	177,892	2.7%	47	2.5%
Germany	47	3.1%	54,794	0.8%	61	3.2%
Italy	332	21.6%	592,812	8.9%	426	22.5%
Spain	101	6.6%	659,558	9.9%	127	6.7%
Hungary	47	3.1%	559,413	8.4%	58	3.1%
Czech Republic	16	1.0%	52,840	0.8%	32	1.7%
Israel	53	3.4%	233,226	3.5%	74	3.9%
China	245	15.9%	815,755	12.3%	265	14.0%
South Korea	226	14.7%	2,060,048	31.0%	298	15.7%
Taiwan	37	2.4%	60,445	0.9%	43	2.3%
India	173	11.2%	475,182	7.2%	194	10.2%

Manufactured based on the investigation and review report (March 2013) on evaluation criteria etc., for improving the reliability of generic drugs in FY2012

No. of Review Products

Fiscal Year	New Generic drugs		Drugs under Partial Changes	
	Application	Approval	Application	Approval
FY 2010	1,247	1,011	1,815	1,622
FY 2011	1,154	1,185	1,738	1,906
FY 2012	1,764	1,539	2,313	1,882
FY 2013	1,467	1,438	2,424	2,066
FY 2014	1,166	1,325	2,286	2,122

Review time for new generic drugs

Targets for reducing review time

- Regarding pharmaceuticals which applications were submitted after April 1, 2004, the target review times for the items approved in respective fiscal years, shall be as shown in the following table. The regulatory authority shall make efforts to achieve these targets with the cooperation of the applicants.
- The review system shall be enhanced to achieve these targets.

1. Review time for new application of generic drugs

The following targets shall be achieved at 50% (median) by FY 2018.

Product	Regulatory review time
New generic drugs	10 months

FY 2015
8.2 months

Review time of application for partial change approval (1)

Targets for reducing review time

- Review time of application for partial change approval in generic drugs

The following targets shall be achieved at 50%(median) by FY 2018

Products	Total review time
Drugs applied for partial change approval (change in procedure of study, etc.)	6 months
Drugs applied for partial change approval (expedited reviews)	3 months

FY 2014 6.9 months
(as for regulatory review and inspection time 4.5months)

FY 2015 4.8 months
(as for regulatory review and inspection time 3.6months)

For products to which the review in the Mfg. Method Column described based on amended PAL has been already completed.

Review time of application for partial change approval (2)

Targets for reducing review time

- Review time of application for partial change approval in generic drugs

Targets shall be achieved at 50%(median) by FY 2018, based on the following plan

Fiscal Year	Total review time
FY 2014	15 months
FY 2015	14 months
FY 2016	13 months
FY 2017	12 months
FY 2018	10 months

FY 2014
15.7 months
(as for regulatory review and inspection time 7.7months)

FY 2015
13.0 months

Synthetic Steps of New Drug Substances Approved by MHLW in FY2014

Approximately 40 chemical products were examined, 20% of which were manufactured with convergent manufacturing process. A synthetic step means a formation or a cleavage of covalent bonds, but does not include salt-formation/breaking steps.

Typical number of steps for Registered Process

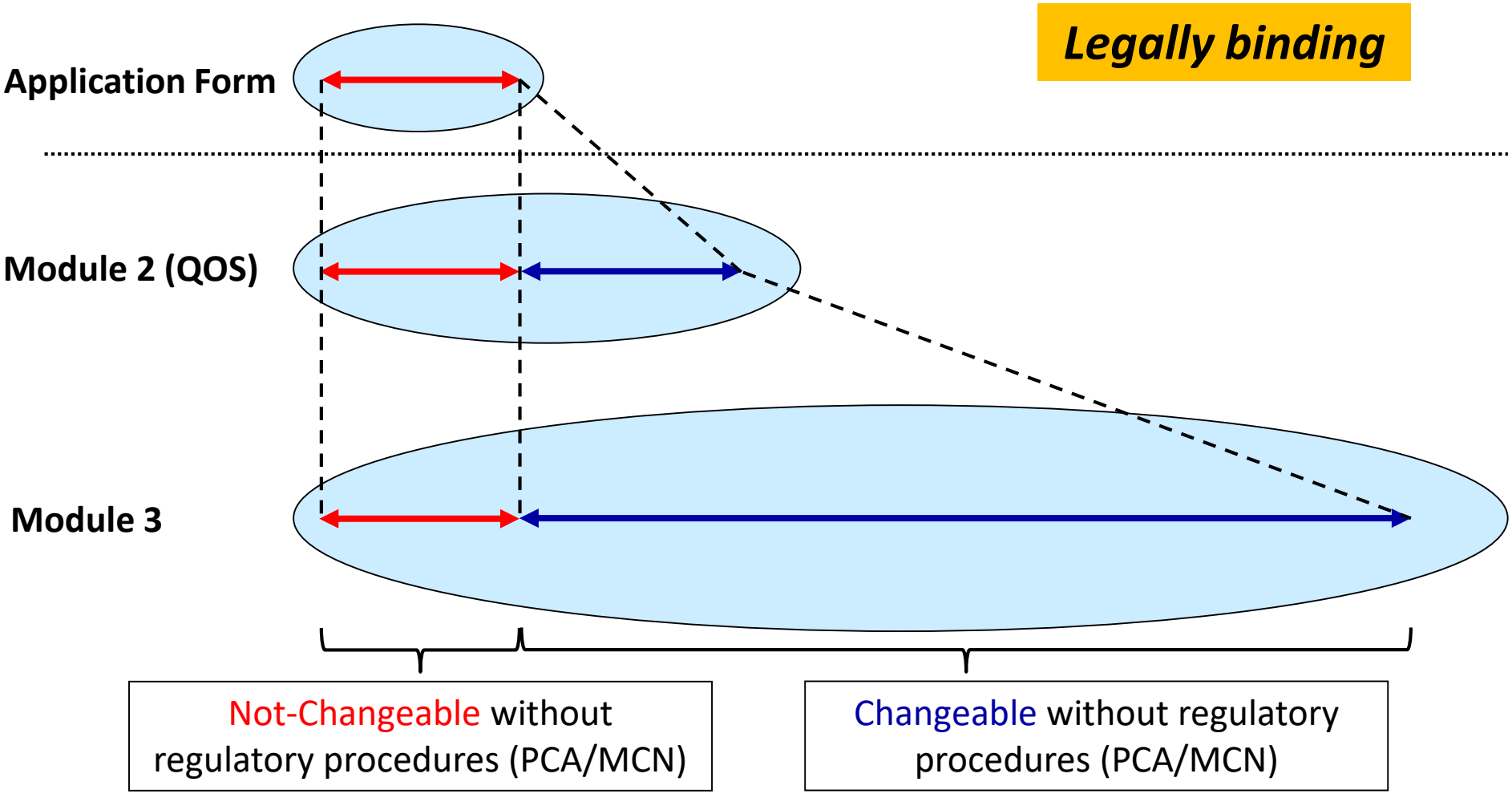
4 steps (30 %)
5 steps (25 %)

outlier
Minimum : 1 steps
Maximum : 14 steps

30% of applications are subjected to redefinition of SM through their review processes

A minimum number of steps is not expected to be registered at PMDA.

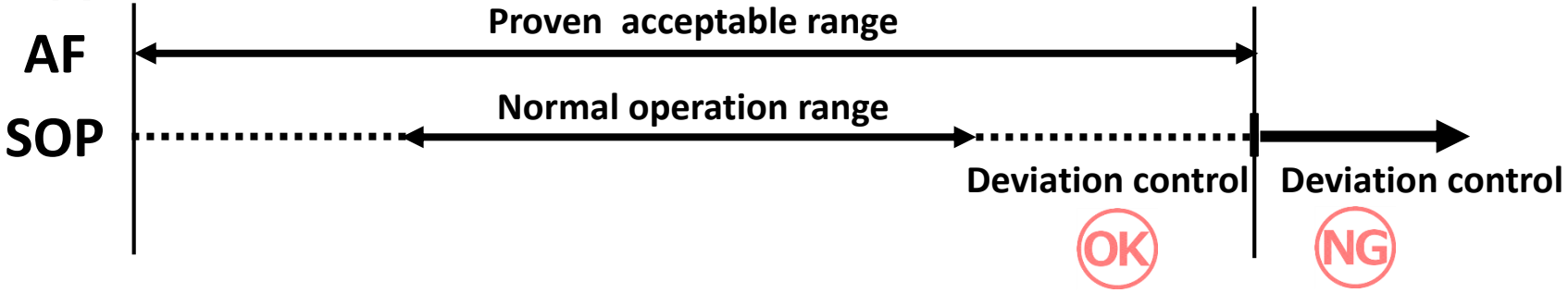
Japan's Effective/Efficient/Flexible Quality Regulation



target/set value (Output/Input value)

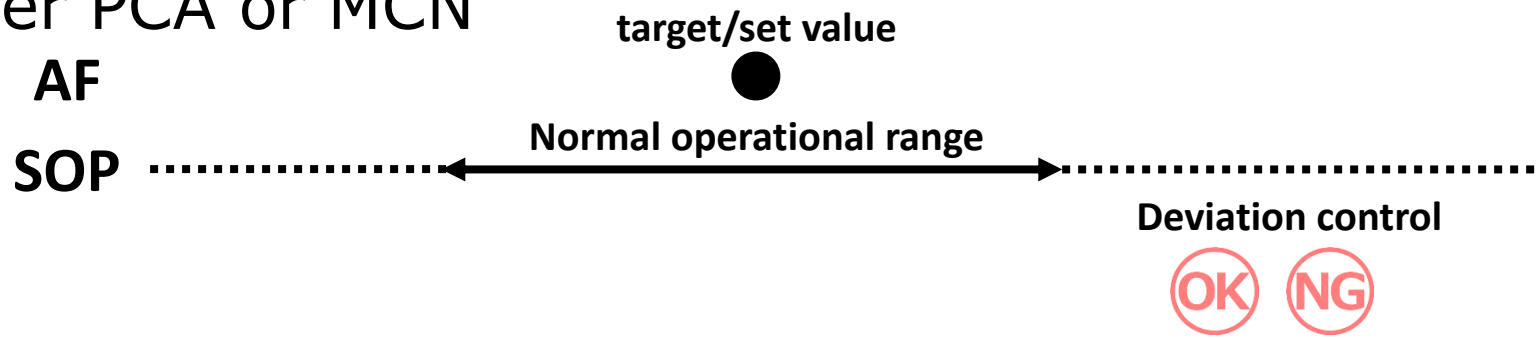
- Range description

For parameters significantly affects quality (e.g. viral safety), PCN



- One point description

For target/set values, standard amounts of charge, either PCA or MCN



depends on root cause analysis, impact analysis etc.

GMP inspection authorities (1)

- **MHLW**

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

- **PMDA**

Pharmaceuticals and Medical Devices Agency

- **47 Prefectures**

Hokkaido, Aomori, Akita, Yamagata, Iwate, Miyagi, Fukushima, Tochigi, Gunma, Ibaraki, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Nagano, Yamanashi, Shizuoka, Aichi, Gifu, Toyama, Ishikawa, Mie, Fukui, Shiga, Nara, Wakayama, Kyoto, Osaka, Hyogo, Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Kochi, Ehime, Fukuoka, Oita, Miyazaki, Saga, Nagasaki, Kumamoto, Kagoshima and Okinawa.

GMP inspection authorities (2)

GMP Inspection Manual

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

MHLW

（manufacturing license, marketing license, marketing authorization, administrative order, pharmacovigilance, license withdrawal, seizure, penalty, etc.）

- **Control inspectorates**
- **Ultimate responsibility**

Delegate MHLW's authorities by Law/Ordinance

PMDA
Pharmaceuticals and Medical Devices Agency

(Inspectorate)

PMDA is partially vested with authorities of MHLW (assessment , GMP inspection, information gathering)

Prefectures

(47 Inspectorates)

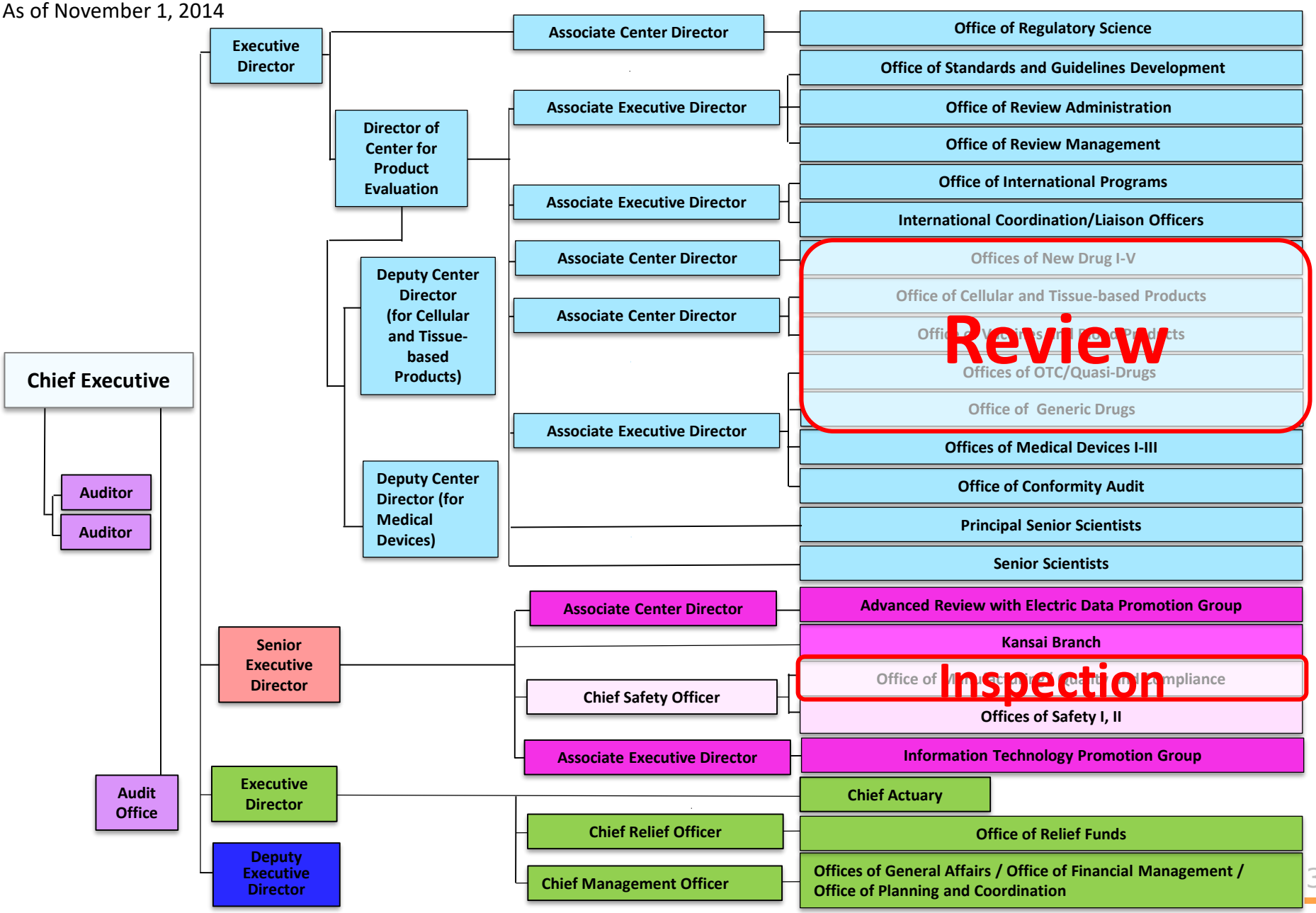
Prefectures are delegated with part of MHLW's authorities for their administrative jurisdictions

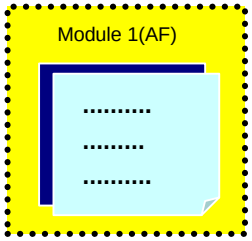
Authorities of GMP inspection

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	pmda Pharmaceuticals and Medical Devices Agency	pmda Pharmaceuticals and Medical Devices Agency
Other Drugs	**47 Pref. Gov.**	pmda Pharmaceuticals and Medical Devices Agency

Organization Chart of PMDA

As of November 1, 2014





Matters to be described in manufacturing field of AF

All processes from raw material(s) to packaging process

- A flow diagram of manufacturing process including:
  - ・Raw materials ・Charge-in amount ・Yield
  - ・Solvent ・Intermediate materials
  - ・Process parameter (e.g. Target Value/Set Value)

- A narrative description of manufacturing process
  - Acceptance criteria of starting material(s) and intermediate materials
  - In process control, Design Space and RTRT etc.

- Enter items other than target/set values in・・
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