Session 1
Regulatory Review & Updates

Japan regulatory system for pharmaceutical products and Active Pharmaceutical Ingredients

Pharmaceuticals and Medical Devices Agency (PMDA)

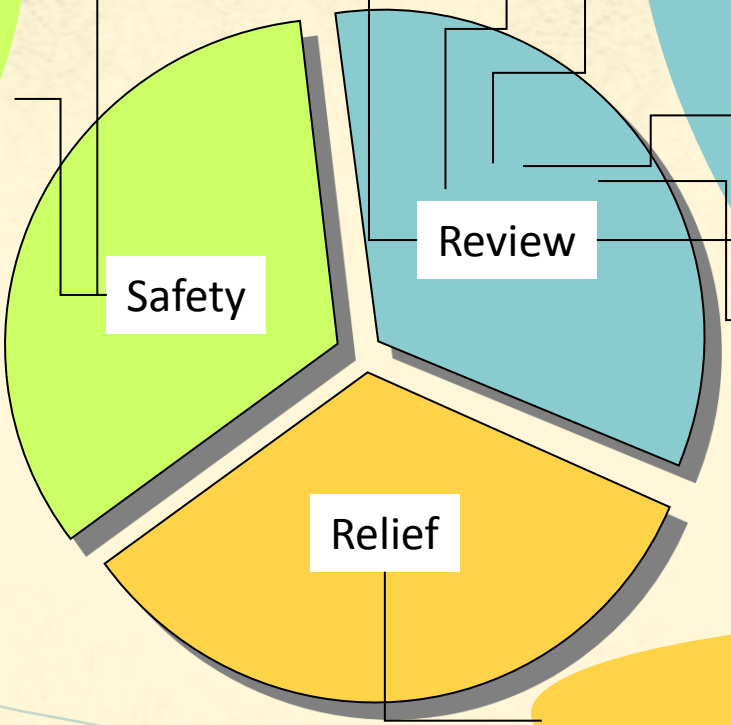
Office of New Drug Ⅱ

Hiroaki Yamada

Today's Topics

1. New Drug Review by PMDA
   - Review system and application data for new drugs
   - Post-marketing safety measures for new drugs
2. Measures taken for overcoming Drug lag
   - additional indication for off-label use
   - Utilization of foreign data by bridging
   - Multi-regional clinical trials (MRCT)
   - Study Group on Unapproved and Off-label Drugs
3. Current Activities

Organization of PMDA



Office of Safety I & II

Office of Manufacturing /Quality and Compliance

Office of Review Administration,
Office of Review Management

Office of New Drug I～V

Office of Cellular and Tissue-based Products,
Office of Vaccines and Blood Products

Office of OTC/General Drugs

Office of Medical Devices I～III

Office of Non-clinical and Clinical Compliance

Office of Relief Fund

Main tasks of the New Drug Review Team

1） Consultation

- Consultation in the development stage (mainly clinical trial consultations)
- Conducted by the review team in charge of the product after application

2） Review

- Review team reviews the application data and make scientific evaluations on approval
- Creation of review reports

Organization of Review Team

Office Director

↑↓

Review Director

Review Team

Specification, stability, Pharmacology, ADME	Toxicity	Clinical	Statistics	Management/ control
2～3 members Pharmacy	2～3 Veterinary	2～3 Medical	1～2 （Biostatistics	2～3 Medical, Pharmacy

Job Assignment at the Office of New Drug

Office of New Drug I	Area 1 Area 6-2	Gastrointestinal drugs, Dermatologic drugs Hormone drugs, Drugs for metabolic disorders (including diabetes mellitus, osteoporosis, gout, and inborn errors of metabolism)
Office of New Drug II	Area 2 Area 5 Radiopharmaceuticals In-vivo Diagnostics	Cardiovascular drugs, Antiparkinson drugs, Antithrombotics, Anti-Alzheimer's drugs Reproductive system drugs, Drugs for urogenital system, Combination drugs Radiopharmaceuticals Contrast Media
Office of New Drug III	Area 3-1 Area 3-2	Central nervous system drugs, Peripheral nervous system drugs (excluding anesthetic drugs) Anesthetic drugs, Sensory organ drugs (excluding drugs for inflammatory diseases), Narcotics
Office of New Drug IV	Area 4 Area 6-1 AIDS Drugs	Antibacterial drugs, Vermifuge, Antifungal drugs, Antiviral drugs (excluding AIDS drugs) Respiratory tract drugs, Anti-Allergy drugs (oral administration only), Sensory organ drugs (inflammatory diseases) Anti-HIV Drugs
Office of New Drug V	Antineoplastic	Antineoplastic Drugs
Office of Cellular and Tissue-based Products	Cellular and Tissue-based Products Bio-CMC	Cell therapy, Regenerative medicine, Gene therapy, Quality of biological products, confirmation of compliance to Cartagena Act
Office of Vaccines and Blood Products	Vaccines Blood Products	Vaccines, Antitoxic serum Blood products

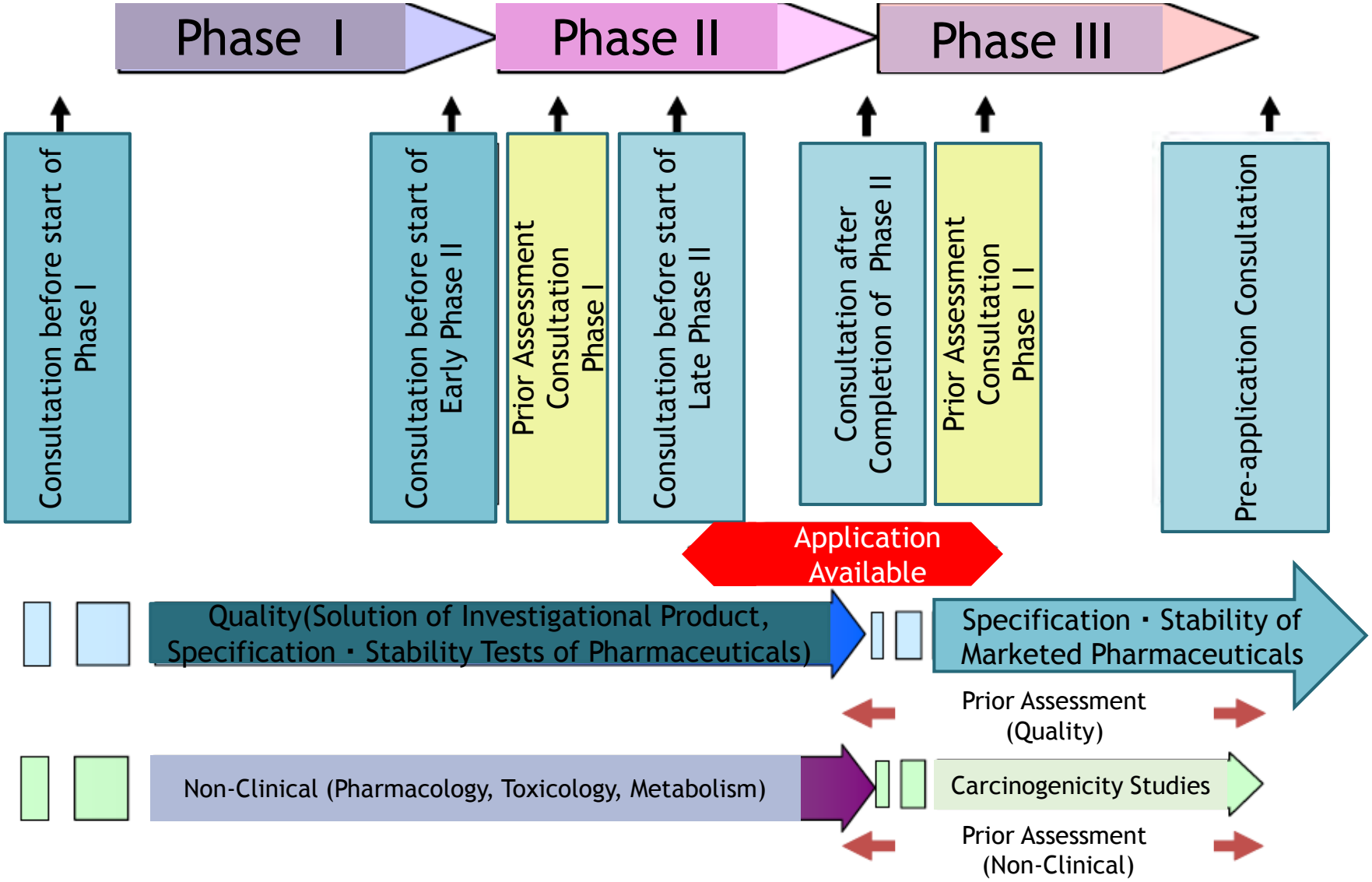
Contents of Consultation

- Decision on the overall development plan
- Problem solving for non-clinical toxicity studies
- Problem solving for first in human studies
- Problem solving on clinical trial design such as dose selection studies and confirmatory studies
- Problem solving on Clinical Data Package for application
- Prior assessments on study results (Prior Assessment Consultation)

Etc.

Timeline of Clinical Trial Consultation and Prior Assessment Consultation

(Image : Timeline of Prior Assessment Consultation is not defined)



Drug Review

Confirmation of the product that it is not applicable to cases where an approval shall not be granted by law.

Review and approval in terms of the PMD Act

(Law for ensuring the quality, efficacy, and safety of drugs and medical devices)

- Article 14

  Persons intending to market a drug, quasi-drug, some of the cosmetics, or medical devices must obtain approval of the MHLW for marketing of each item.

- Article 14 paragraph 2

  Approvals shall not be granted when any of the following conditions apply

（→ cases where an approval shall not be granted ）

Cases where an approval shall not be granted

- Article 14 paragraph 2 (3)

1 The drug, quasi-drug, or medical device is not shown to possess the indication or properties indicated in the application

2 The drug, quasi-drug, or medical device in the application is found to have no value as the products mentioned by the harmful actions which significantly outweigh the indication

3 In addition to the cases indicated in the preceding two items, the drug, quasi-drug, cosmetics or medical device is designated by MHLW Ordinance as not being appropriate as a drug, qasi-drug, cosmetic, or medical device.

Approved Product Information in Japan
（Main Contents on Application Form）

① Brand Names of Pharmaceuticals

② Ingredients and Quantities or Nature of Pharmaceuticals

③ Manufacturing Method of Pharmaceuticals

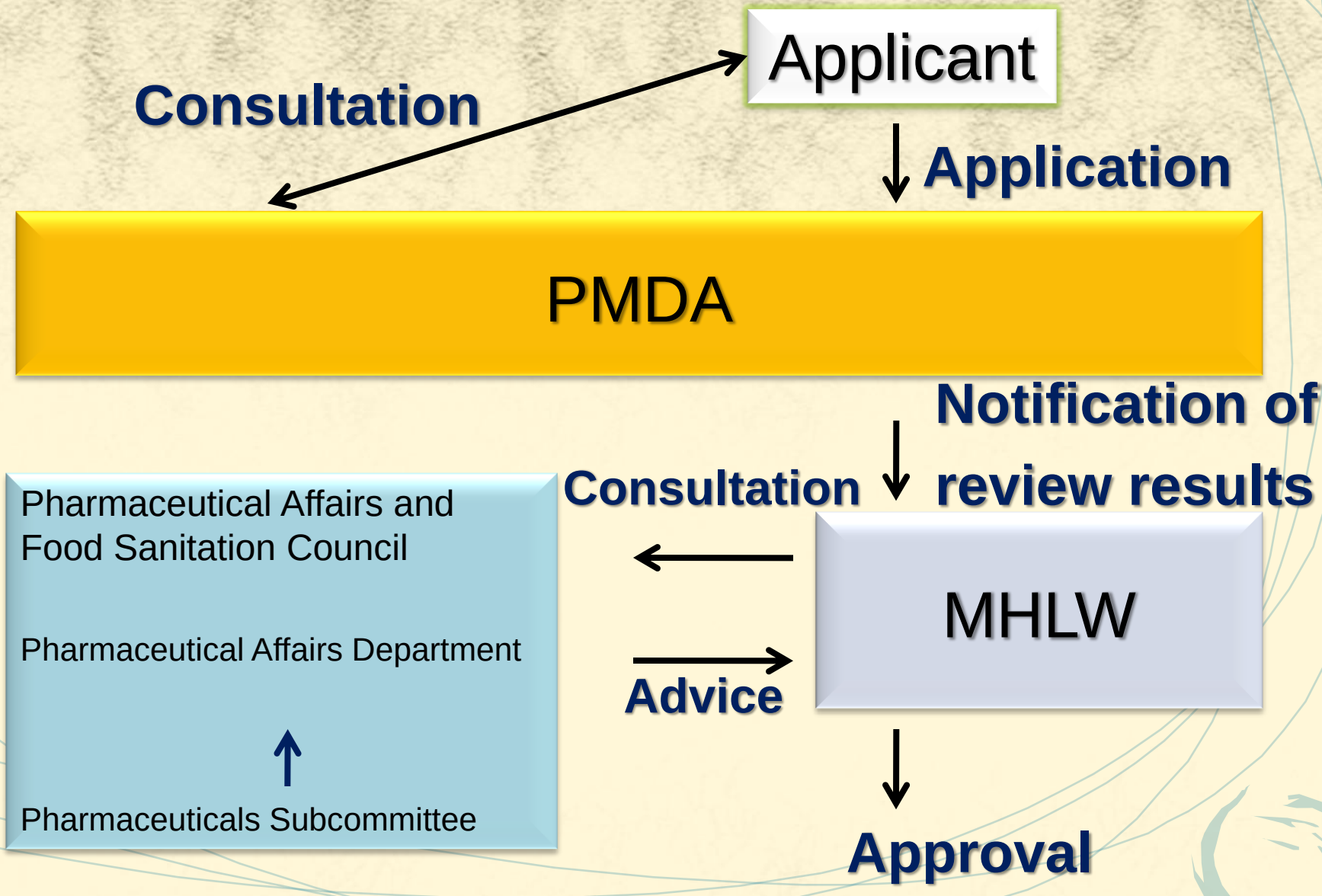
④ Dosage and Administration of Pharmaceuticals

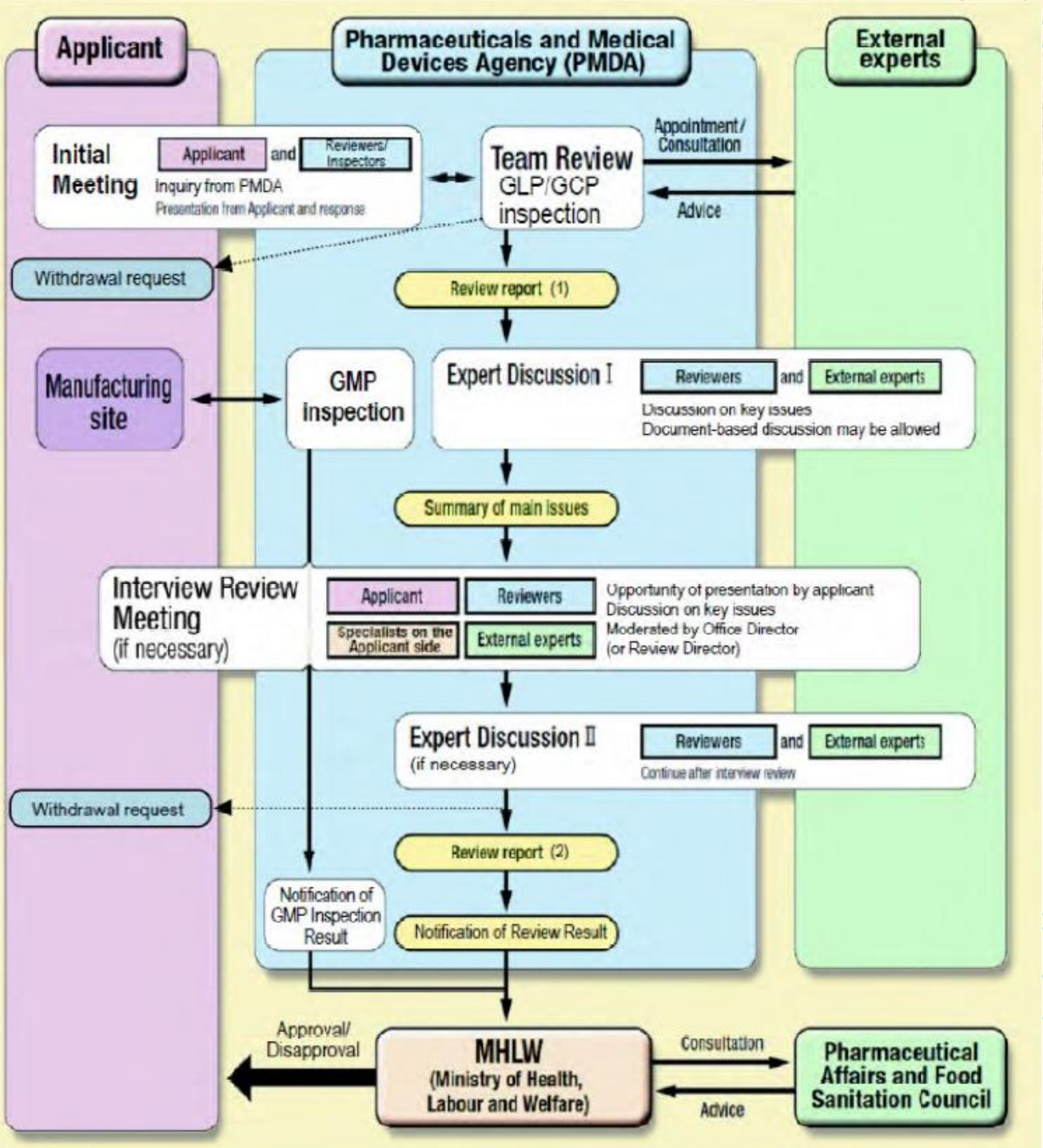
⑤ Indications of Pharmaceuticals

⑥ Storage Statement or Shelf Life of Pharmaceuticals

⑦ Specifications of Pharmaceuticals

New Drug Application Review Flowchart




Applicant
Pharmaceuticals and Medical Devices Agency (PMDA)
External experts
Initial Meeting
Applicant
and
Reviewers/ Inspectors
Inquiry from PMDA
Presentation from Applicant and response
Team Review
GLP/GCP inspection
Appointment/ Consultation
Advice
Withdrawal request
Review report (1)
Manufacturing site
GMP inspection
Expert Discussion I
Reviewers
and
External experts
Discussion on key issues
Document-based discussion may be allowed
Summary of main issues
Interview Review Meeting
(if necessary)
Applicant
Reviewers
Specialists on the Applicant side
External experts
Opportunity of presentation by applicant
Discussion on key issues
Moderated by Office Director
(or Review Director)
Expert Discussion II
(if necessary)
Reviewers
and
External experts
Continue after interview review
Withdrawal request
Review report (2)
Notification of GMP Inspection Result
Notification of Review Result
Approval/ Disapproval
MHLW
(Ministry of Health, Labour and Welfare)
Consultation
Advice
Pharmaceutical Affairs and Food Sanitation Council

Composition of Review Reports

- Review Results
  Final decision of review
- Review Report（１）
  Summary of Submitted data and review
  Main points of contents of the Expert Discussion
- Review Report（２）
  Results from the Expert Discussion

Uploaded on the PMDA Homepage after approval

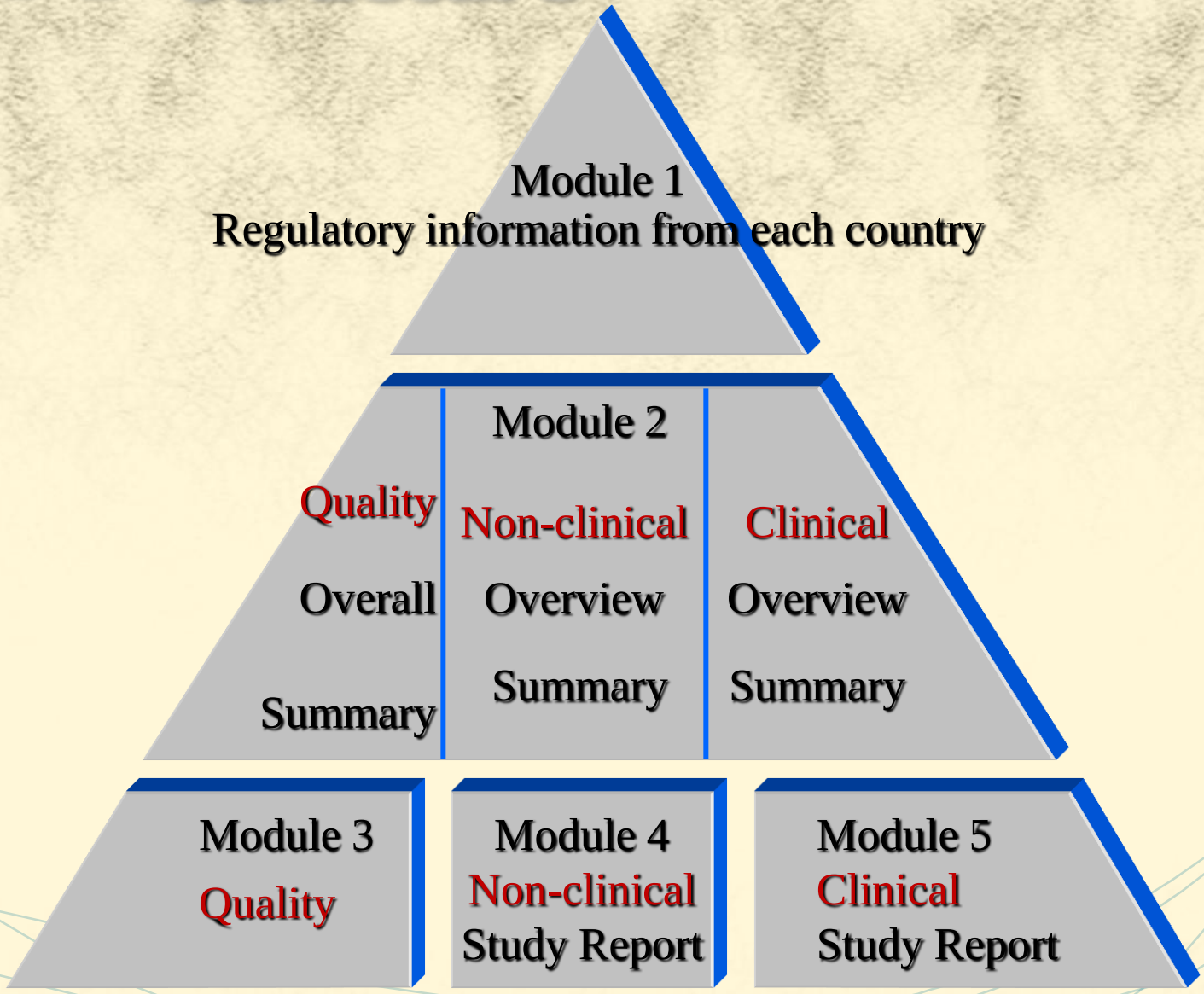
Application Data for New Drug

Common format in the US, EU, and Japan

Common Technical Document

C T D

C T D Structure



CTD Module 1 （Japan）

- Product application form (copy)
- Origin of history of discovery and usage conditions in foreign countries
- List of other drugs in the class
- Instruction of use (draft)
- Documents on classification for poisonous or powerful or other products
- Post-Marketing Surveillance Basic Protocol (draft)

CTD Module 2（Summary）

Summary on data relating to quality

Summary of data on Non-clinical study

- **Pharmacology studies**
- **Pharmacokinetic studies**
- **toxicity studies**

Summary of data on Clinical study

- **Clinical pharmacology studies**
- **Clinical studies（efficacy, safety）**

Post-marketing System

Re-examination system

Post-marketing surveillance etc.

Re-evaluation system

Re-evaluation of quality, efficacy, and safety of approved drugs by current scientific standards.

Adverse reaction/infection reporting system

Revision of package insert based on collected reports providing safety information.

Types of Post-marketing Surveillance

- **Post-marketing sureveillance**

  Ascertain the incidence of serious adverse reactions that require special attention and promote the proper use of drugs for 6 months after marketing

- **Use-results survey**

  Surveys under daily use in clinical practice

  all-case surveillance：for all cases that had been treated

- **Specified use-results survey**

  Pediatrics, elders, pregnant/parturient women, hepatic/renal impairment, long term use, etc.

- **Post-marketing clinical study**

Risk Management Plan (RMP)

Products approved after April 1st, 2013

- **Safety Specification**

  Summary of important identified risks of a drug, important potential risks, and important missing information
- **Pharmacovigilance Plan**

  Plan for post-marketing surveys/studies that are conducted to collect information based on the identified "Safety Specifications
- **Risk Minimization Plan**

Re-examination Period

- Drugs with new active ingredient
  ・・・・・・・・8 yrs
- Drugs with new combination, new route of administration
  ・・・・・・・・6 yrs
- Drugs with new indication
  ・・・・・・・・4 yrs
- Orphan drugs
  ・・・・・・・10 yrs

※ Approval of generics is prohibited during re-examination periods

Post-marketing System

Re-examination system

Post-marketing surveillance etc.

Re-evaluation system

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Adverse reaction/infection reporting system

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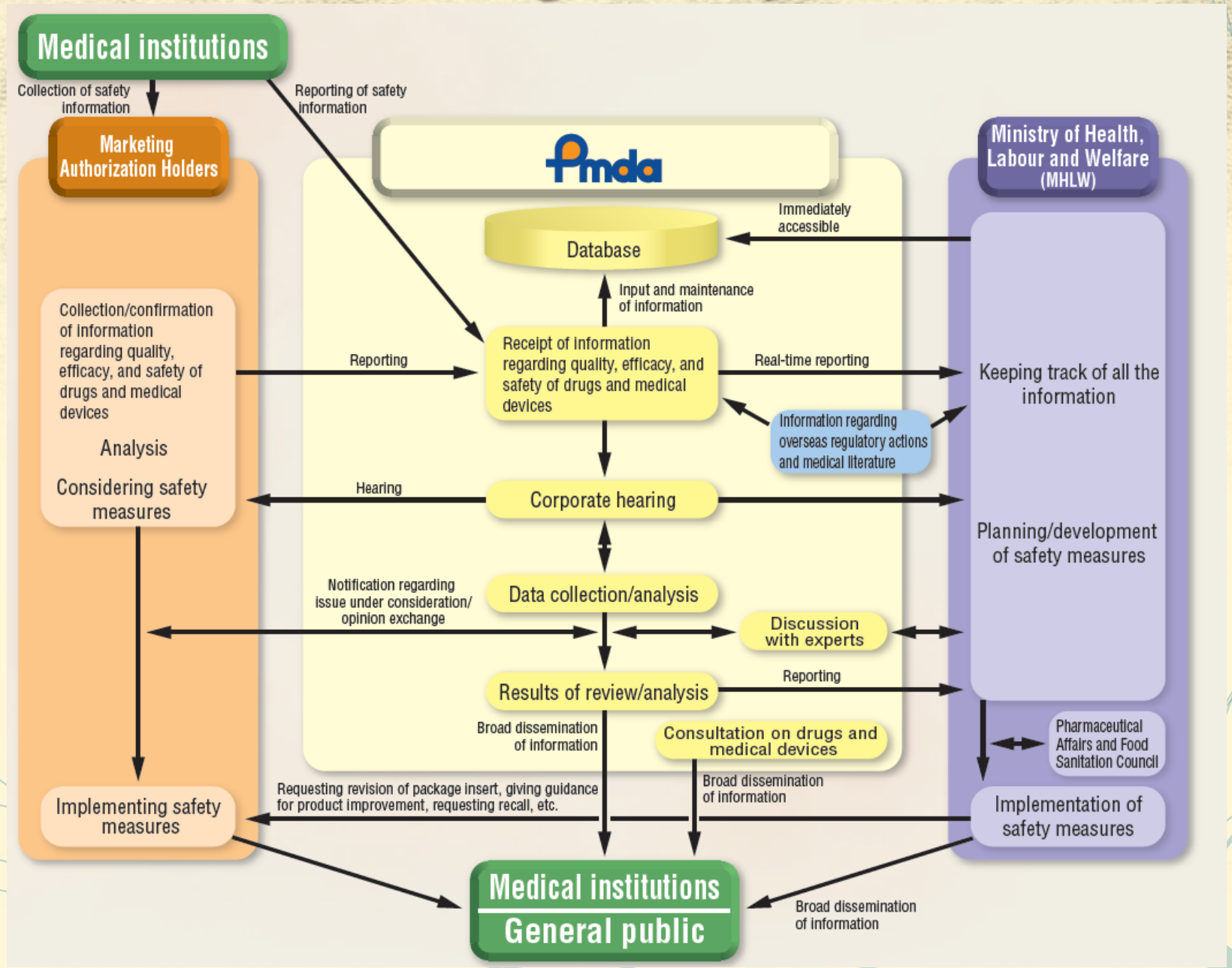
Post-marketing Safety Measures



PMDA Medi-Navi

（ Pharmaceuticals and medical devices information e-mail service ）

- **Dear Healthcare Professional letter, Blue Letter**
- **Notification on revision of Package insert and labelling**
- **Information on recalls**
- **Information on approvals**
- **Information on drug related risks that are being assessed**

etc.

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What is Drug lag?

The situation in which drugs used in overseas is not approved in Japan and hence could not be used in Japan

Application lag: delayed application to Japan

Review lag: longer review time compared to overseas

Drug lag = Application lag + Review

The cause of drug lag in Japan

- Lengthy duration of total review time from application to approval
- Time taken for development is lengthy in Japan (study data of Japanese patients is mandatory for application)
- Development in Japan is postponed

Measure for Drug lag（１）
Resolution of Issues on Off-label Use

研　　第　　４号
医薬審第　１０４号
平成１１年２月１日

各都道府県衛生主管部（局）長　殿

厚生省健康政策局研究開発振興課長

厚生省医薬安全局審査管理課長

適応外使用に係る医療用医薬品の取扱いについて

薬事法による製造又は輸入の承認を受けている医薬品であって、当該医薬品が承認を受けている効能若しくは効果以外の効能若しくは効果を目的とした又は承認を受けている用法若しくは用量以外の用法若しくは用量を用いた医療における使用（以下「適応外使用」という。）が行われているものについては、最近の厚生科学研究においてその科学的根拠の評価が実施されているところである。
これら適応外使用に係る医療用医薬品であって当該適応外使用に十分な科学的根拠のあるものについて、医療の中でより適切に使用されるためには、当該適応外使用

Resolution of Issues on Off-label Use

- **Approved and used as a standard treatment in overseas (stated in international guidelines and/or text books)**
- **Sufficient evidence available from foreign clinical studies etc.**
- **The product has been approved and used for an off-label use in another indication in Japan.**

Abbreviate clinical studies and approve as medical and pharmaceutical public knowledge

Off-label use example: Aspirin（treatment for thrombotic disease）

【Background】

- Approved as an antipyretic, analgesic, and antiphlogistic in Japan
- Low-dose aspirin is approved as a standard treatment for thrombotic disease in overseas
- Pediatric formulation was used as an off-label use thrombotic disease treatment for adults in Japan as well

Off-label use example:
Aspirin（treatment for thrombotic disease）

【Indication at application】

- Acute stroke or transient ischemic attack (TIA)
- Acute myocardial infarction
- Prevention for the recurrence of myocardial infarction
- Unstable angina
- Stable angina

Off-label use example:
Aspirin（treatment for thrombotic disease）

【Review materials】

- Publications on pharmacological action（several）
- Review articles of internationally reliable scientific journals（several）
- Record in textbooks of international standard（several）
- Therapeutic guidelines by international academic conferences（several）
- WHO publication
- Approval contents of US and Europe
- Status of off-label use in Japan

Off-label use example:
Aspirin（treatment for thrombotic disease）

【Indication at approval】

- Inhibition of thrombus, embolus formation for the following disease:

  Angina（Chronic stable angina、Unstable angina）

  Myocardial infarction

  Ischemic cerebrovascular disease （Transient ischemic attack (TIA)、Stroke）

- Inhibition of postoperative thrombosis, embolism in coronary artery bypass grafting (CABG) or Percutaneous transluminal coronary angioplasty (PTCA)

Measures for Drug lag（２）

Utilization of foreign clinical data（ICH E5 Guideline）

医薬審第６７２号
平成１０年８月１１日

各都道府県衛生主管部（局）長　殿

厚生省医薬安全局審査管理課長

外国臨床データを受け入れる際に考慮すべき民族的要因について

外国で実施された臨床試験データの医薬品の製造（輸入）承認申請に当たっての取扱いについては、平成１０年８月１１日医薬発第７３９号厚生省医薬安全局長通知「外国で実施された医薬品の臨床試験データの取扱いについて」により通知されたところである。これにより、一定の条件に適合する外国臨床データについては医薬品の製造（輸入）承認申請書に添

Utilization of Foreign Data

- **Evaluation of effects of ethnic factors on efficacy of drugs**

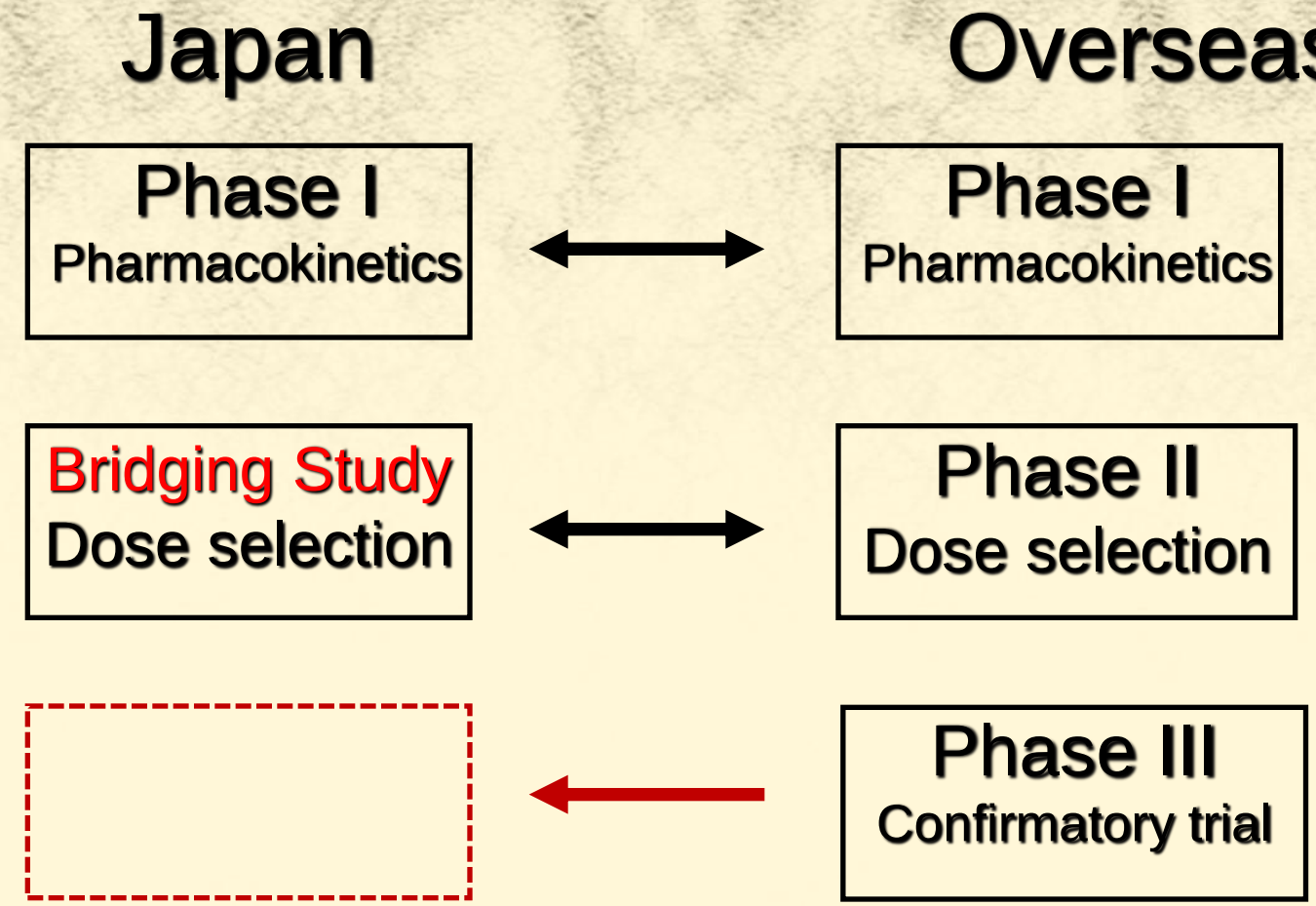
  Extrinsic factor（Environment、Medical background）

  Intrinsic factor（Genetic polymorphism、BMI）

- **Comparison of pharmacokinetics and dose response between Japanese and foreign populations**

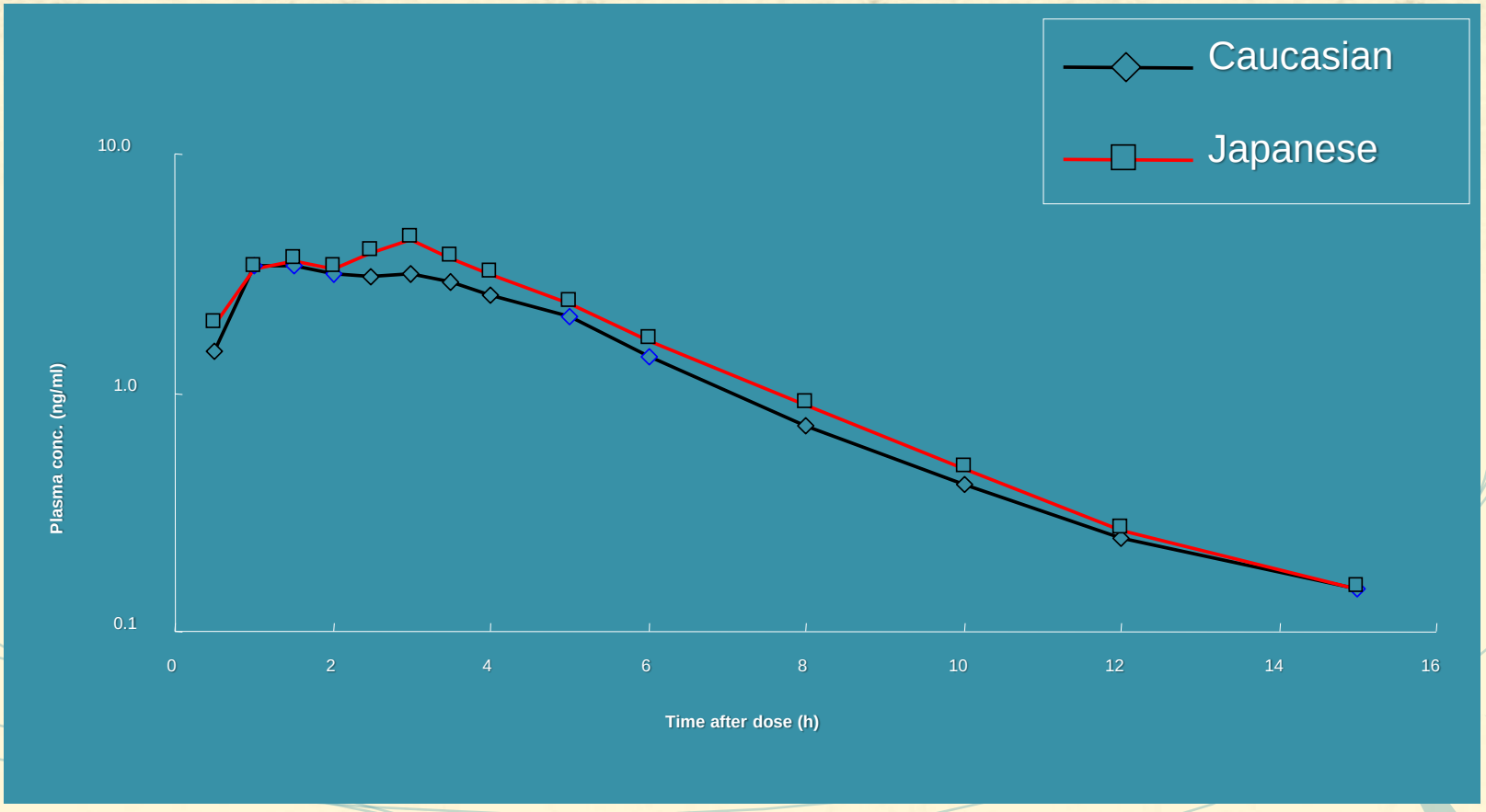
Extrapolation of foreign data in Japanese population（Bridging）

Typical case in Bridging Study



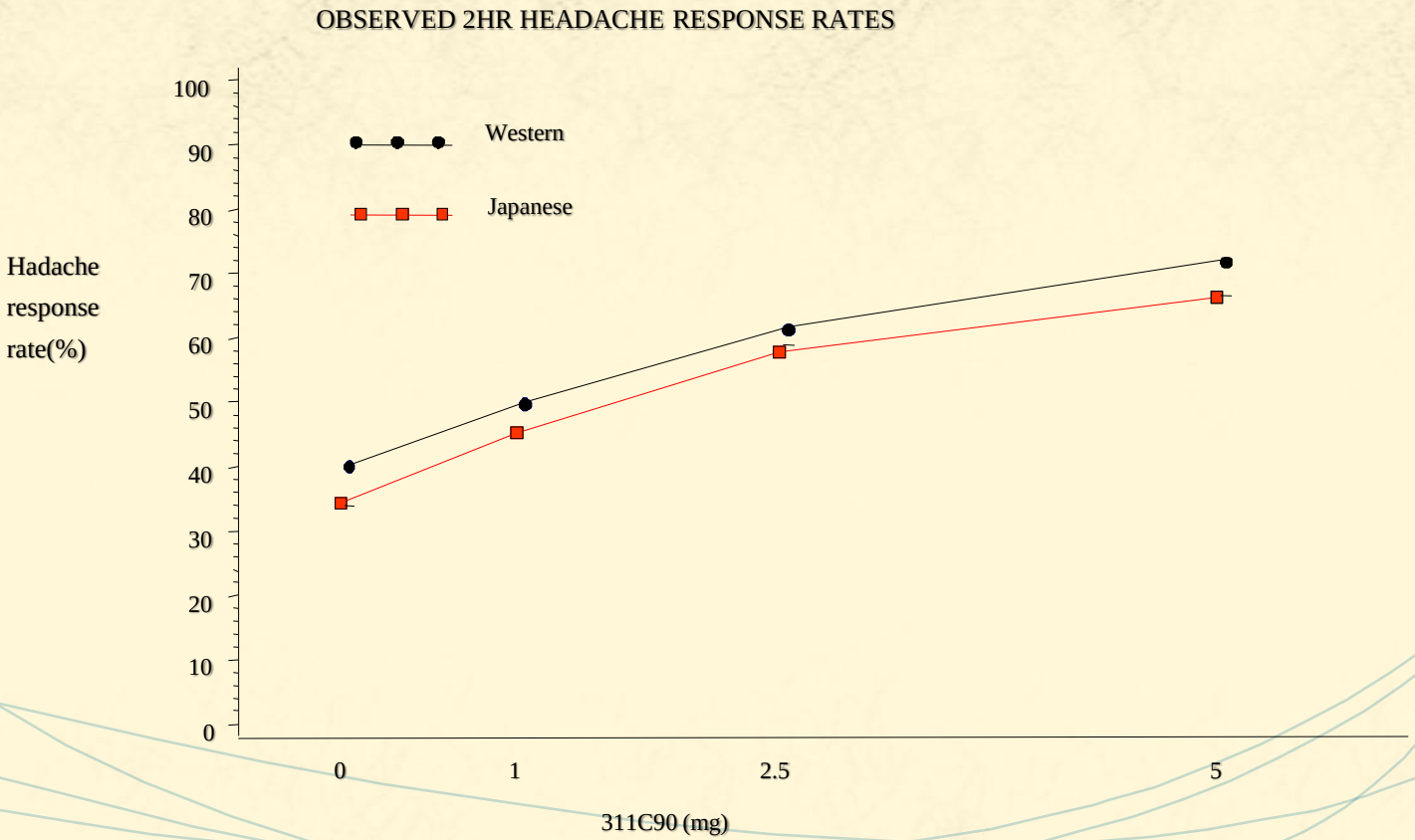
Example of Bridging Study:
Zolmitriptan（Migraine treatment）

Phamacokinetics



Example of Bridging Study: Zolmitriptan（Migraine treatment）

Dose response



Example of Bridging Study: Zolmitriptan（Migraine treatment）

Clinical Data Package of Bridging Study

Domestic

Phase I（single dose, multiple dose） 2 studies

Comparative Pharmacokinetics with Caucasians 1 study

Bridging Study (Phase II） 1 study total: 4 studies

Foreign

Phase I（single dose, multiple dose） 2 studies

Phase II 2 studies

Phase III 2 studies total: 6 studies

Effects on drug lag reduction by bridging:

2 years (approx.)

Reduction is limited since bridging study begins after foreign studies are complete

For further drug lag reduction:

Concurrent development

participation in

Multi-Regional Clinical Trial (MRCT)

Measures for Drug lag（３）

Participating in Multi-Regional Clinical Trial(MRCT)

薬食審査発第0928010号
平成１９年９月２８日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

国際共同治験に関する基本的考え方について

従来、我が国においては、ＩＣＨ－Ｅ５ガイドラインに基づく「外国臨床データを受け入れる際に考慮すべき民族的要因について（平成10年8月11日医薬審第762号 厚生省医薬安全局審査管理課長通知）」により、いわゆる「ブリッジング」による海外臨床試験成績を承認申請資料として活用することを認めており、また、欧米諸国における市販後調査等の結果についても必要に応じ承認審査に際して活

Points to Consider for Multi-regional Clinical Trial (MRCT)

- As for bridging, effects of ethnic factor on the efficacy of drug must be evaluated.
- Similarities must be confirmed in the dose-response curve and PK data between Japanese and non-Japanese population.
- Japanese subjects must be incorporated in order to confirm consistency in the data of total population and Japanese population.

MRCT example:
Indacaterol（COPD）

【Foreign multi-regional Phase II/III Study】

- Placebo and active-controlled double-blind study
- Adaptive seamless design

Stage 1 : 2 dosages are selected from the following, by the rules set by the Efficacy and Safety Assessment Committee

75、150、300、600 μg

Stage 2 : Efficacy is evaluated from the two selected dosages

↓

150 and 300 μg were chosen in Stage 1

MRCT example: Indacaterol（COPD）

【Foreign multi regional Phase II/III Study】

Stage 2

Primary endpoint：trough FEV_1 after 12 weeks of dosage

表 10　投与 12 週後のトラフ FEV_1（L）のプラセボ群との比較（ITT 集団）

	プラセボ群	本剤 150 μg 群	本剤 300 μg 群	Tio 群
被験者数**	376	389	389	393
平均値±標準偏差	1.30±0.47	1.47±0.54	1.51±0.57	1.37±0.52
LS mean±標準誤差*	1.28±0.015	1.46±0.015	1.46±0.015	1.42±0.015
群間差* [98.75%信頼区間]*	—	0.18 [0.14, 0.22]	0.18 [0.14, 0.22]	0.14 [0.10, 0.18]
p 値*	—	<0.001***	<0.001***	<0.001

*: 混合効果モデル、 トラフ FEV_1= 投与群 + ベースラインの FEV_1 + SABA による可逆性成分 + 抗コリン薬による可逆性成分 + 喫煙歴 + 国 + 実施医療機関+ 誤差、実施医療機関は国の入れ子の変量効果。

**: モデル解析に寄与した被験者数。

***: プラセボ群に対する本剤群の優越性は、p 値が多重性を調整した両側有意水準 0.0125 より小さく、かつ 98.75%信頼区間の下限が 0 L より大きい場合に成立する。

MRCT example: Indacaterol（COPD）

【Asian multi-regional Phase III study】

- Placebo-controlled double-blind study
- Japan, Korea, Taiwan, India, Hong Kong, Singapore
- Dose：Placebo, 150 μg、300 μg
- Primary endpoint：trough FEV_1 after 12 weeks of dosage
- Total population: 347cases

  Japanese population: 152cases（44% of total population）

MRCT example: Indacaterol（COPD）

【 Asian multi regional Phase III study 】

[Total population]

表 5　投与 12 週後のトラフ FEV_1（L）のプラセボ群との比較（ITT 集団）

	プラセボ群	本剤 150 μg 群	本剤 300 μg 群
被験者数***	104	109	110
平均値±標準偏差	1.16±0.41	1.41±0.46	1.35±0.45
LS mean±標準誤差*	1.17±0.025	1.34±0.024	1.37±0.023
群間差 [95%信頼区間] *	—	0.17 [0.13, 0.21]	0.20 [0.16, 0.24]
p 値*, **	—	<0.001	<0.001

*: 混合効果モデル、 トラフ FEV_1 = 投与群 + ベースラインの FEV_1 + 短時間作用型 β_2 刺激薬（SABA） による可逆性成分 + 抗コリン薬による可逆性成分 + 喫煙歴 + 国 + 実施医療機関+ 誤差、実施医療機関は国の入れ子の変量効果。
**: p 値の大きい群より順に比較を行う、Hochberg のステップアップ法に基づく閉手順により、 多重性を考慮。
***: モデル解析に寄与した被験者数。

[Japanese population]

表 7　投与 12 週後のトラフ FEV_1（L）のプラセボ群との比較（日本 ITT 集団）

	プラセボ群	本剤 150 μg 群	本剤 300 μg 群
被験者数**	43	49	48
平均値±標準偏差	1.12±0.37	1.46±0.45	1.40±0.51
LS mean±標準誤差*	1.17±0.021	1.38±0.020	1.40±0.020
群間差 [95%信頼区間] *	—	0.20 [0.15, 0.26]	0.23 [0.17, 0.28]

*: 混合効果モデル、 トラフ FEV_1 = 投与群 + ベースラインの FEV_1 + SABA による可逆性成分 + 抗コリン薬による可逆性成分 + 喫煙歴 + 実施医療機関+ 誤差、実施医療機関は変量効果。
**: モデル解析に寄与した被験者数。

MRCT example:
Indacaterol（COPD）

- The results of the Asian multi-regional Phase III study was the reproduction of the foreign multi regional Phase II/III study.
- No conflicts observed in the results of efficacy and safety between the total population and the Japanese population.
- No significant disparity observed in the efficacy and safety between 150 μg and 300 μg doses

【Approved dosage】

The usual adult dosage is one capsule (150 μg as Indacaterol）administered once daily via an inhaler device

MRCT example: Indacaterol（COPD）

Comparison of approved doses

EU （approved in 2009）

150～300 μg inhaled once daily

Japan （approved in 2011）

150 μg inhaled once daily

US （approved in 2011）

75 μg inhaled once daily

MRCT example: Indacaterol（COPD）

The Risks and Benefits of Indacaterol — The FDA's Review

Badrul A. Chowdhury, M.D., Ph.D., Sally M. Seymour, M.D., Theresa M. Michele, M.D., Anthony G. Durmowicz, M.D., Dongmei Liu, Ph.D., and Curtis J. Rosebraugh, M.D., M.P.H.

In July 2011, the Food and Drug Administration (FDA) approved Arcapta Neohaler (indacaterol maleate powder), a long-acting beta-agonist (LABA), at a dose of 75 μg once daily as a bronchodilator for patients with chronic obstructive pulmonary disease (COPD).[1] Since the European Medicines Agency (EMA) had approved indacaterol at doses of 150 μg and 300 μg in 2009,[2] one might question why the FDA selected a 75-μg dose.

Historically, LABAs have been developed first for patients with doses and a lower dose (75 μg), and there were safety concerns regarding the proposed doses.

In the original NDA, dose-ranging explorations were limited to an adaptive-design trial that included a 2-week dose-ranging phase with seven treatment groups (four indacaterol groups [75 μg to 600 μg], two active-comparator groups, and a placebo group) followed by a 26-week confirmatory phase. The primary efficacy end point was the forced expiratory volume in one second (FEV_1) greater area under the FEV_1 curve 1 to 4 hours after a dose than that associated both with tiotropium and with formoterol, and that the lowest dose fulfilling the above two criteria and the next-highest dose were to be selected. On the basis of these criteria, 150 μg and 300 μg of indacaterol were chosen for the trial's confirmatory phase. According to the FDA's analyses of the data, all doses of indacaterol were more effective than placebo and had a similar effect size, which

N ENGL J MED 365 (2011)

Measures for Overcoming Drug lag

- Off-label use drugs

  → **Approval by Public Knowledge with abbreviating clinical studies**

- Drugs developed overseas

  → **Development by bridging**

- Drugs that are being developed overseas

  → **Concurrent development by participating in the MRCT**

- **Foreign standard treatments that are not planned to be developed in Japan**

  → Study Group on Unapproved and Off-label Drugs of High Medical Need

Study Group on Unapproved and Off-label Drugs of High Medical Needs

We have publicly asked for requirements to be applied by the following schedule. 1st application from June 18 to August 17 - 2nd from August 2 to September 30 - 3rd from August 1 to December 27 which is closed at the moment for the first session. The second session is scheduled to be closed once at the end of June 2014 for reexamination.

< Requirements from the 2nd application >

- **Unapproved Drugs**

  Approved either in the following six countries (USA, United Kingdom, Germany, France, Canada, Australia).

- **Off-label Drugs**

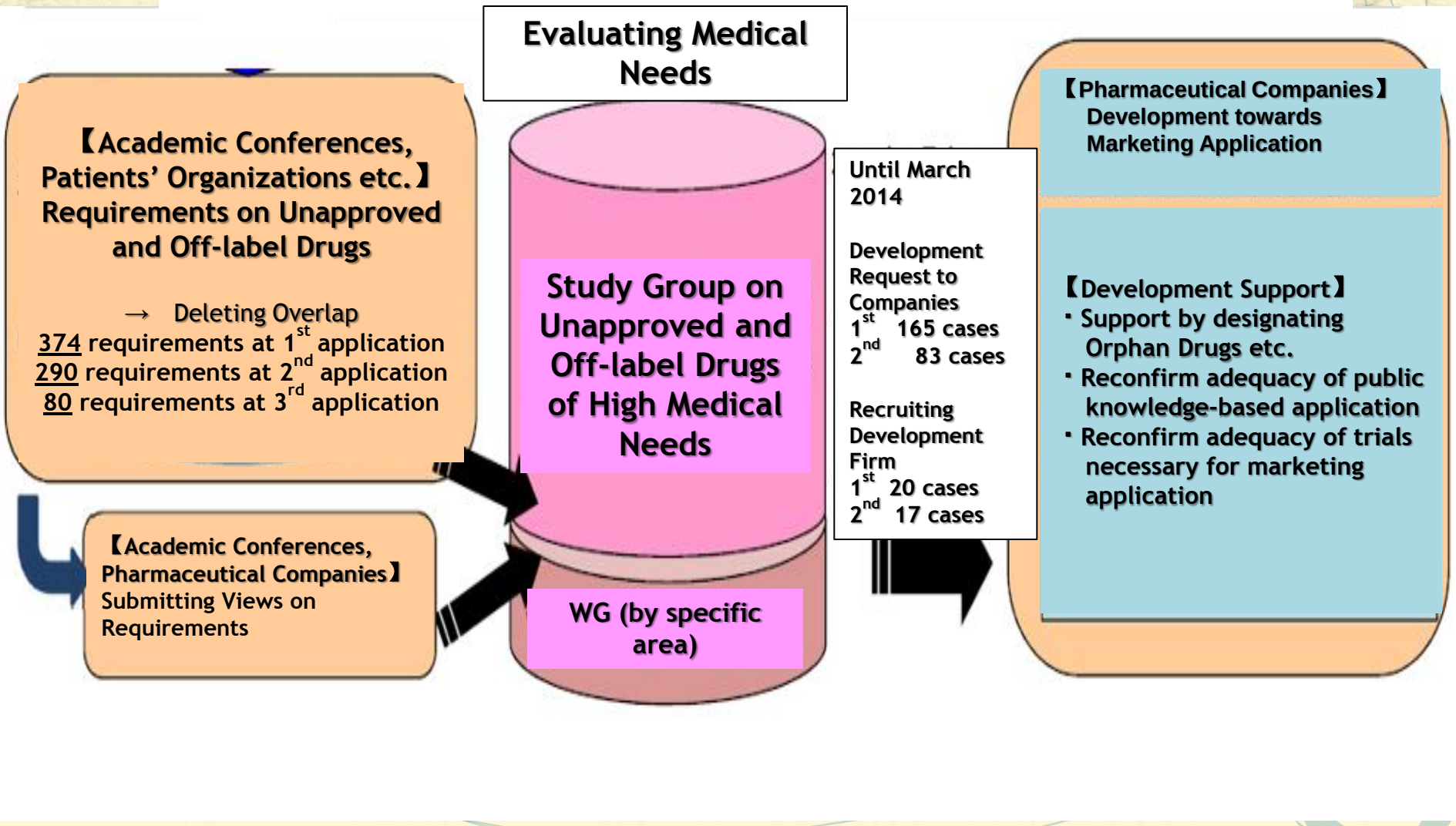
  Approved either in the following six countries (USA, United Kingdom, Germany, France, Canada, Australia) widely used at a particular dosage and dose regimen based on a certain evidence.

Applies to both cases (1) and (2) in "High Medical Needs",

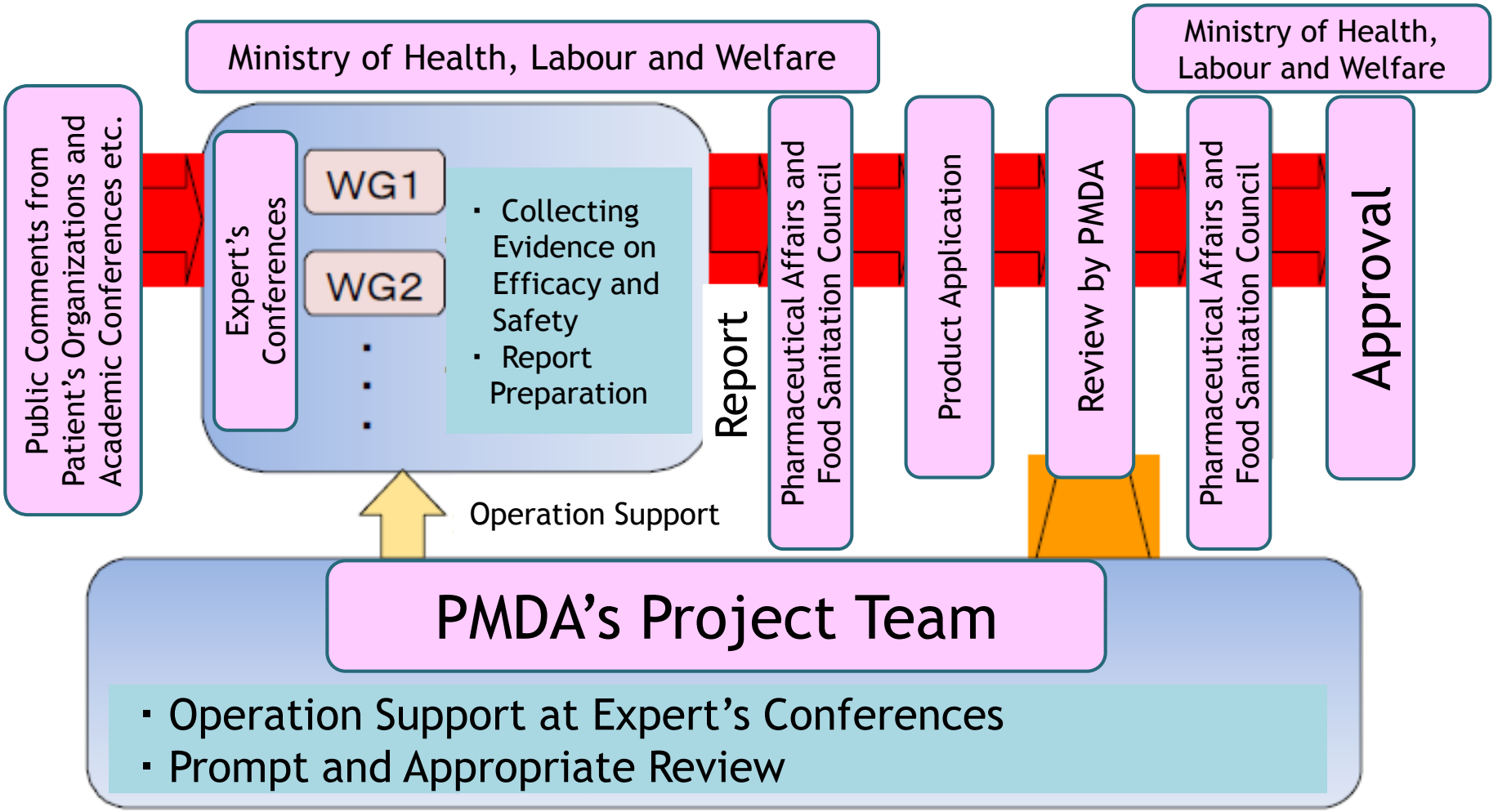
(1)Severity and Progression of the disease is either a) life-threatening or b) irreversible or c) significantly affecting patients' daily lives.

(2)Pharmaceutically useful in : a) cases in which existing treatment is not available in Japan or b) cases in which efficacy and safety assessed by clinical trials in the US and Europe are obviously superior to that of existing treatment or c) cases in which treatment is standardized in the US and Europe, and is expected to provide benefits in Japan even when the differences in each medical environment is taken into account.

Study Group on Unapproved and Off-label Drugs of High Medical Needs



PMDA's Approach Towards Unapproved Drugs etc.



Drugs considered to have high medical Needs by the Study Group

- **Off-label use drugs**

  → Request the corresponding industry for Public Knowledge

- **Drugs unapproved in Japan and used as standard therapy overseas**

  → Request corresponding industry for development

- **Drugs that do not have the corresponding industry**

  → Public offering of developer

Results of evaluation on first demands data（2009.6.18～8.17）

374cases

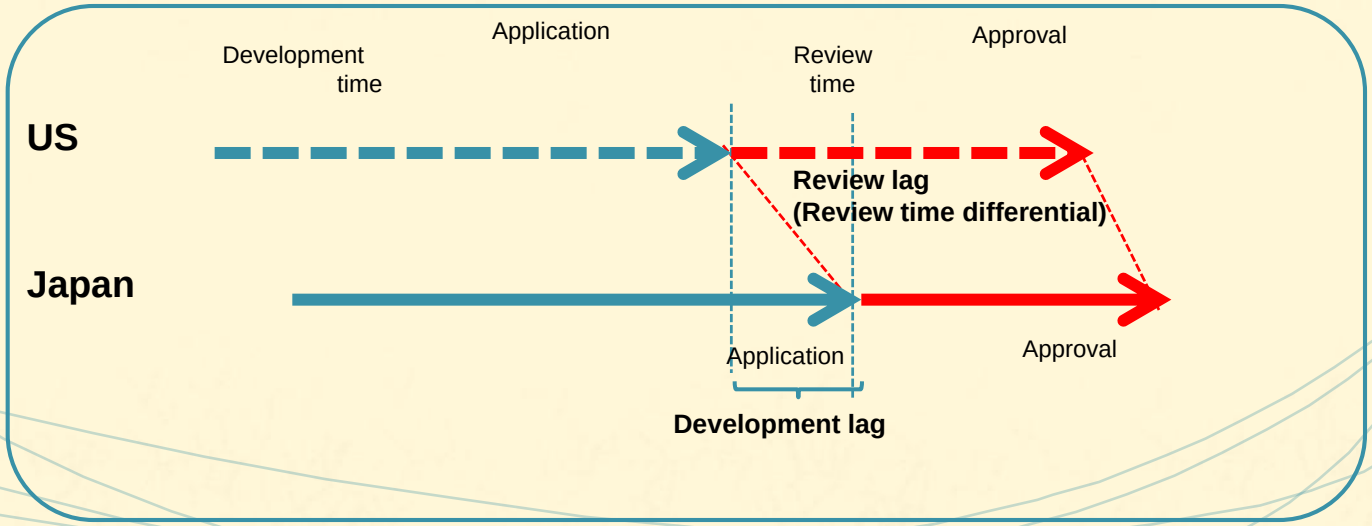
各WGの検討状況			代謝・その他	循環器	精神・神経	抗菌・抗炎症	抗がん	生物	小児	合計	
検討済み	必要性高い	未承認薬	8	9	10	5	10	3	11	56	185
		適応外薬	12	22	21	23	31	2	18	129	
	必要性高くない	未承認薬	4	1	2	0	2	1	1	11	81
		適応外薬	9	4	27	9	18	3	0	70	
海外承認等なし	未承認薬		3	2	3	5	4	0	1	18	104
	適応外薬		12	14	30	9	13	0	8	86	
承認済み	未承認薬		0	0	0	0	1	0	0	1	4
	適応外薬		0	0	2	0	1	0	0	3	
合計			48	52	95	51	80	9	39	374	

High medical needs：185cases
（unapproved 56cases
off-label use 129cases）

Current Trial Calculation of Drug lag

(Year)

	FY 2011	FY2012	FY2013	FY2014
Development Lag	2.5 (2.3)	1.3 (1.0)	1.5 (0.4)	0.3* (0)
Review Lag	0.8	0.4	0.1	0
Drug Lag	3.3 (3.1)	1.7 (1.4)	1.6 (0.5)	0.3* (0)



Today's Topics

1. New Drug Review by PMDA
   - Review system and application data for new drugs
   - Post-marketing safety measures for new drugs
2. Measures taken for overcoming Drug lag
   - additional indication for off-label use
   - Utilization of foreign data by bridging
   - Multi-regional clinical trials (MRCT)
   - Study Group on Unapproved and Off-label Drugs
3. Current Activities

① Development of Innovative Drugs from Japan

Current status and issues

- By the increase of cost and time for development, research for new seeds has become challenging
- In order to develop innovative drugs, constant supply and measures for practical application of promising seeds are necessary.
- Universities and ventures whom have discovered promising seeds have not been able to become a mediator for the seeds to reach the market for practical use.

① Development of Innovative Drugs from Japan

Pharmaceutical Affairs Consultation on R&D Strategy （PMDA）

Consultations on studies and clinical trial designs necessary for academia and ventures after the discovery and selection of innovative medical seeds.

Promote innovative drugs originating from Japan

① Development of Innovative Drugs from Japan

Pharmaceutical Affairs Consultation on R&D Strategy
(Individual Orientations, Pre-Consultation Meetings, Consultations)

Individual Orientations
(Free of Charge)

Explanation on procedures and operations related to Pharmaceutical Affairs Consultation Services by technical experts at the Pharmaceutical Affairs Consultation Group on R&D Studies in preparation for Pre-Consultation Meetings.

Individual Orientations are available anywhere in Japan in case abundant seeds are to be assessed

Is the seed appropriate for Pharmaceutical Affairs Consultation on R&D Strategy?

Universities
Research Institutions
Business Venture

Coordinating Issues

Pre-Consultation Meetings
(Free of Charge)

Main attendance by technical experts, in order to coordinate issues relating to the contents of consultation. Members from the Review Team will join as needed.

Scientific Discussion
(Records are fixed approx. 1 month)

Consultations
(Charged)

Main attendance by Review Team members and Technical experts. Expert Advisor in the specific area will join as needed.

Number of Consultation（2011/7/1～2014/12/31）

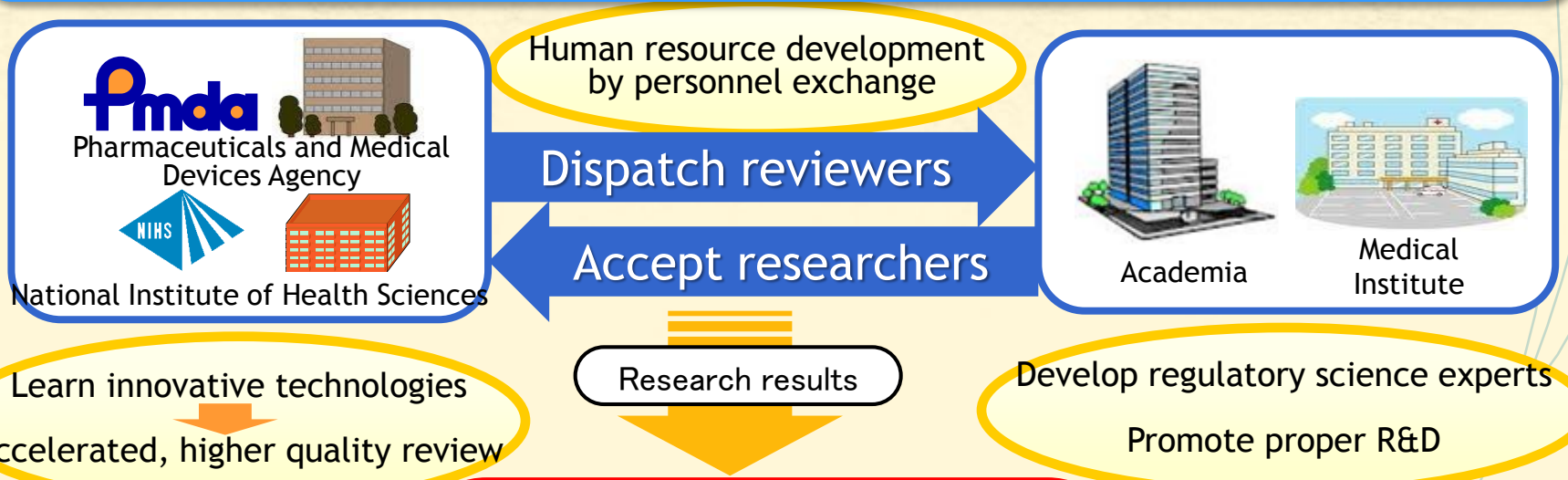
Pre Consultation	Pharmaceutical (except Cell and Tissue base Product)	Medical Devices (except Cell and Tissue base Product)	Cell and tissue based products	Total
University	274	141	112	527 (53%)
Venture company	54	105	145	304 (30%)
Laboratories others	82	26	59	167 (17%)
Total	410 (41%)	272(27%)	316(32%)	166 (100%)

Face to Face Consultation	Pharmaceutical (except Cell and Tissue base Product)	Medical Devices (except Cell and Tissue base Product)	Cell and tissue based products	Total
University	86	29	23	138 (56%)
Venture company	13	17	30	60 (24%)
Laboratories others	33	5	12	50 (20%)
Total	132 (53%)	51 (21%)	65(26%)	248 (100%)

② Exchange of Human Resources

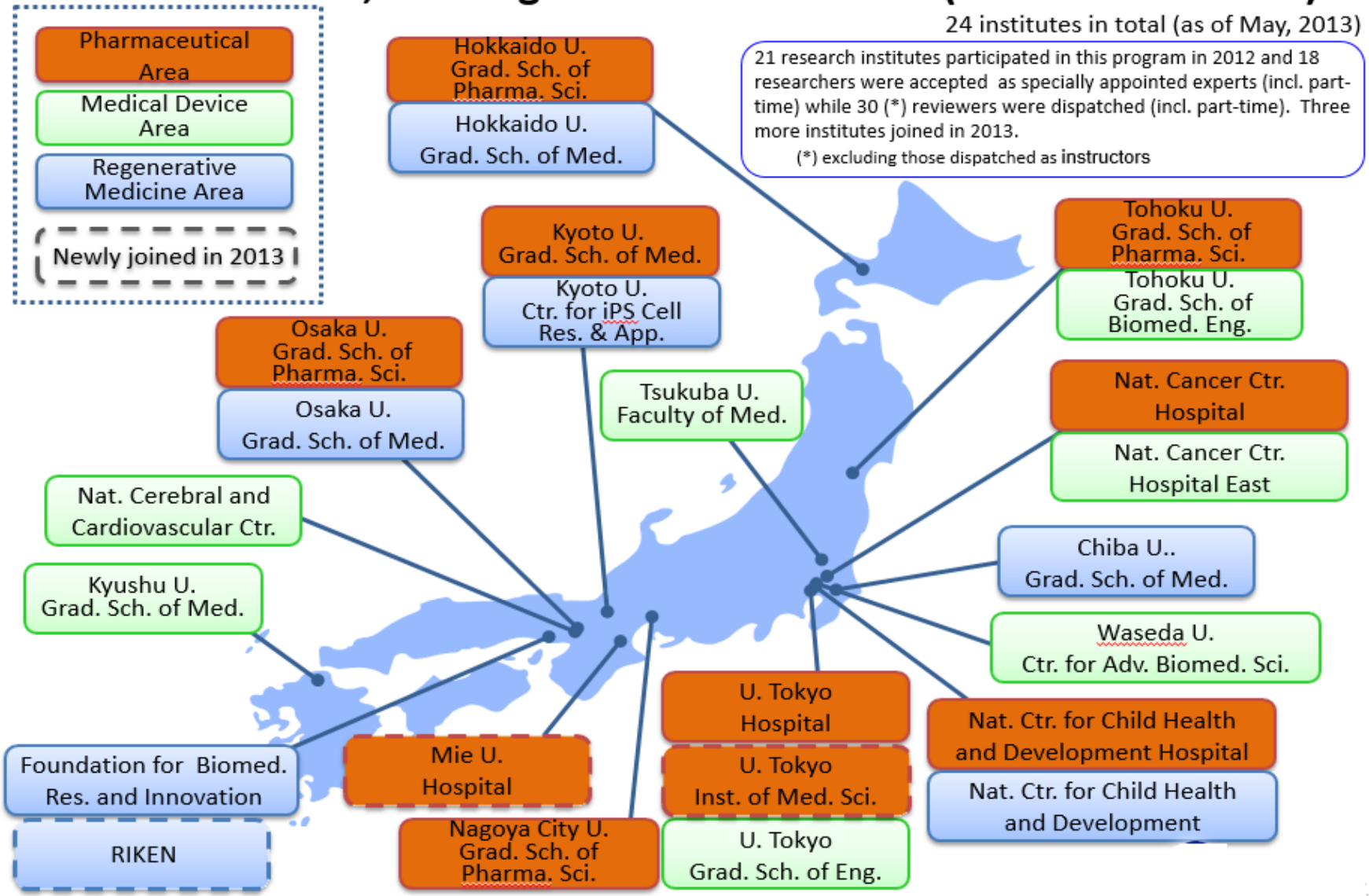
Promotion Program for Practical Use of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medicines (MHLW 2012 budget program)

- Support establishment of regulatory science-based evaluation methodologies for safety and efficacy of products, at academia who are engaged in the research of most advanced technologies.
- Develop regulatory science experts by exchanging personnel between academia and PMDA, National Institute of Health Sciences (NIHS).

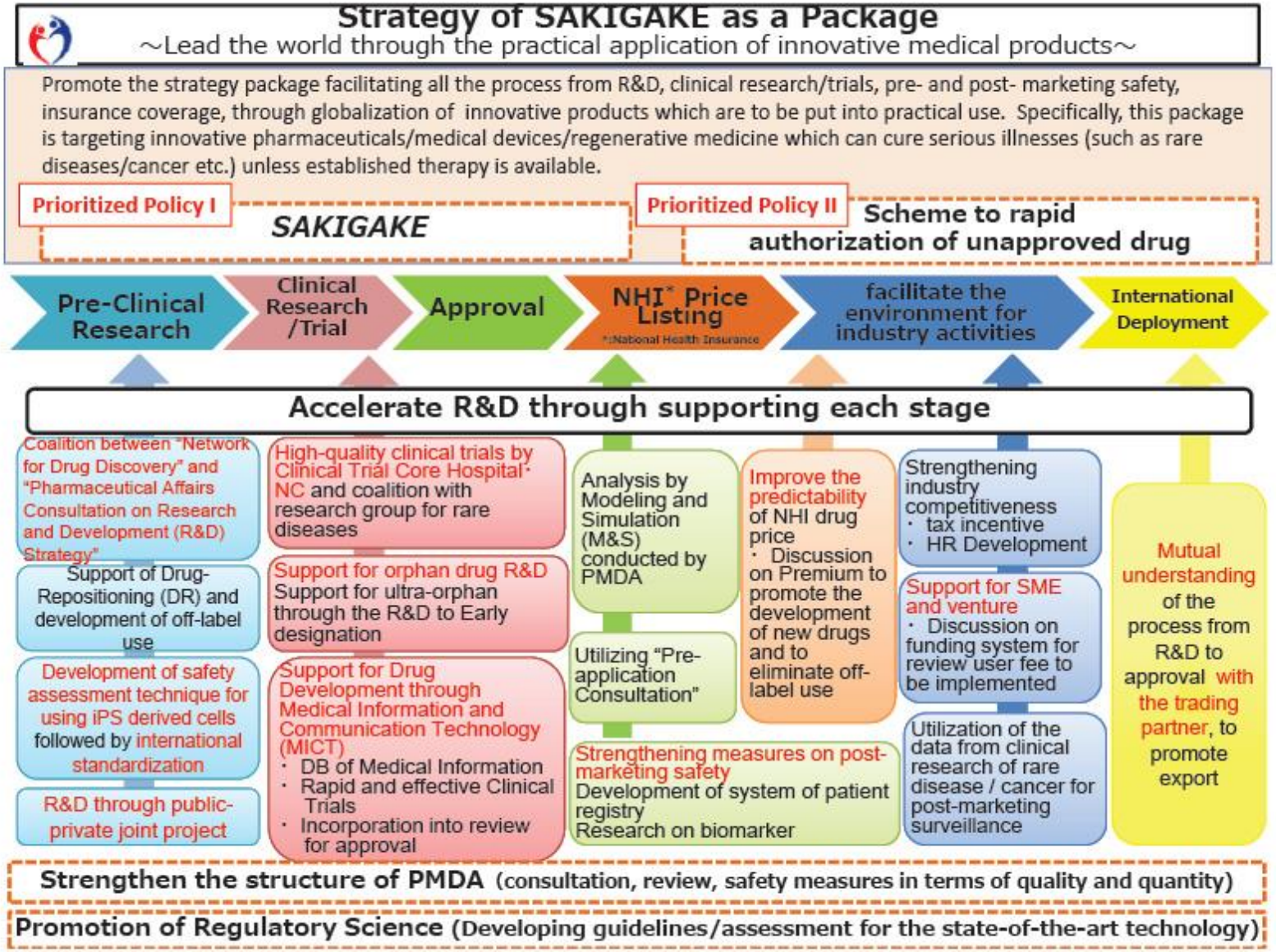


② Exchange of Human Resources

Promotion Program for Practical Use of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medicines (Research Institute)

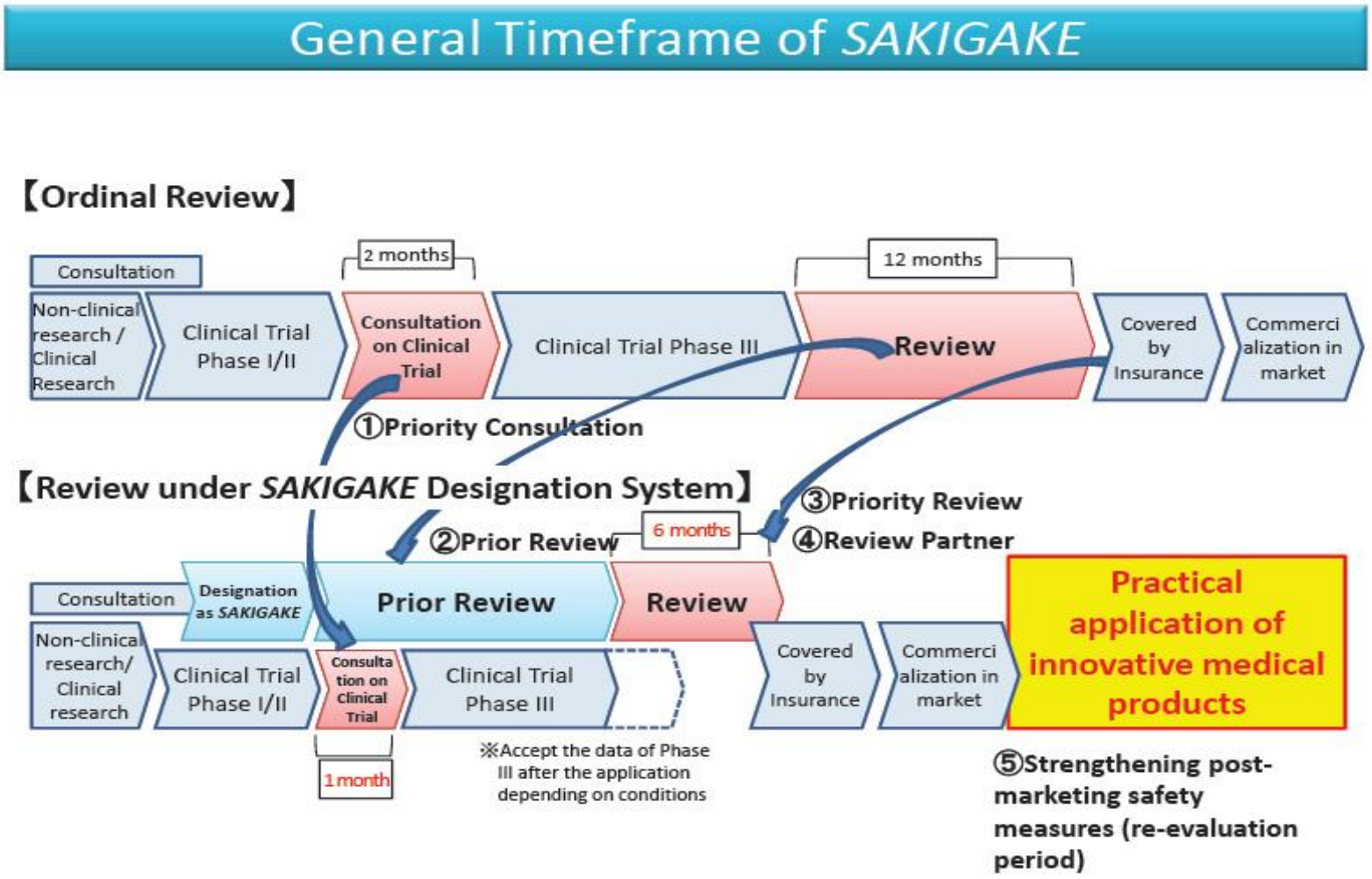


③ Strategy of SAKIGAKE as Package



③ Strategy of SAKIGAKE as Package

Review Under SAKIGAKE Designation System



④ Advancement of Personalized medicine

Drugs that require biomarker testing before administration

Active Pharmaceutical Ingredient	Biomarker
Rituximab(genetic recombinant)	CD20
Trastuzumub(genetic recombinant)	HER2
Imatinib mesylate	Philadelphia chromosome,KIT(CD117), FIP1L1-PDGFRα
Cetuximab(genetic recombinant)	EGFR,KRAS gene
Gefitinib	EGFR gene
Mogamulizumab(genetic recombinant)	CCR4
Crizotinib	ALK fusion gene

④ Advancement of Personalized medicine

Companion Diagnostics

- Appropriate diagnosis before dosage
- Concurrent approval with the drug necessary

Issues

- Simultaneous development of drugs and diagnostics
- Review methods for simultaneous approval

（drugs and medical devices (in-vitro diagnostics)）

→ “Points to Consider for Approval on Companion Diagnostics and Relating Drugs”（July 1st, 2013）

⑤ New technology and methods

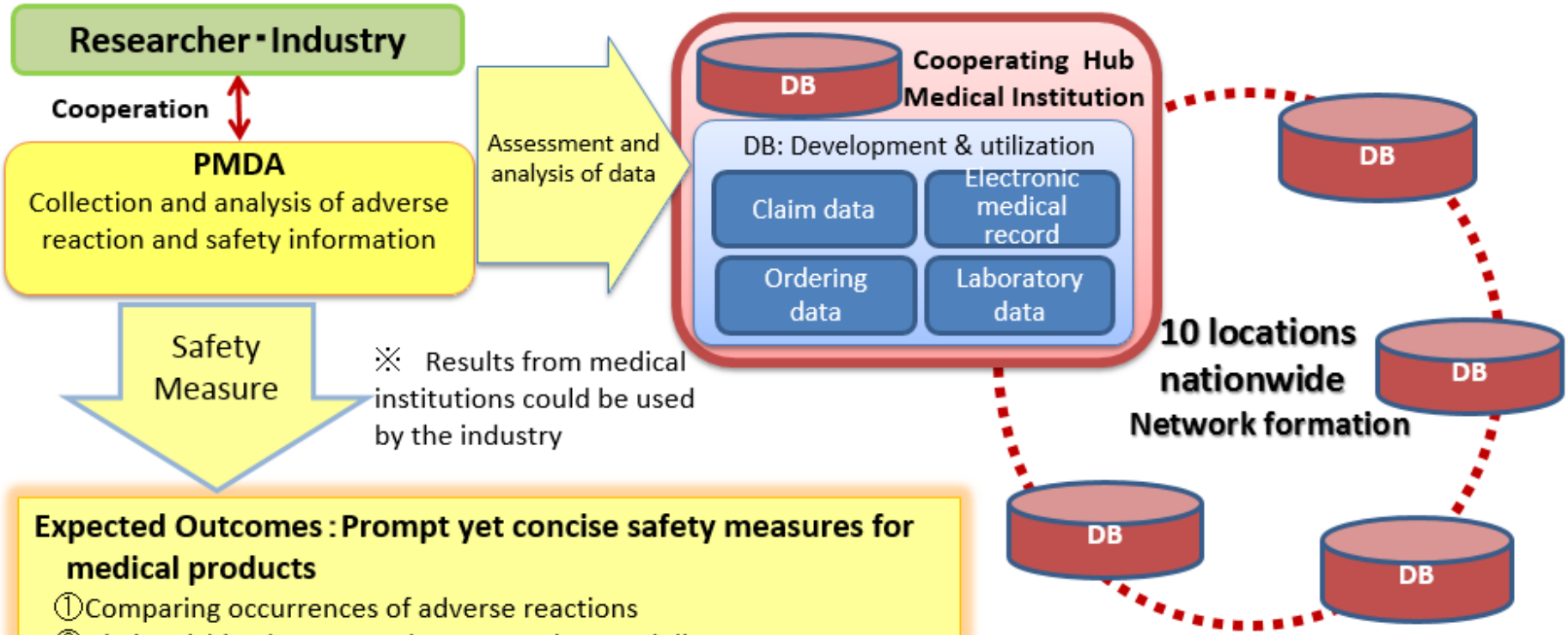
Projects Across Multi-Offices in PMDA

- Microdose Trials Project
- Post-approval Manufacturing Changes Project
- In Vitro Companion Diagnostic Devices Project
- Pediatric and Orphan Drugs Project
- QbD Assessment Project
- Innovative Statistical Strategies for New Drug Development
- Nanomedicine Initiative Project
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Omics Project

⑥ Project for developing the medical information database infrastructure

○Promotion of safety measures based on pharmaco-epidemiological methods for medical products by utilizing medical information DB

○Developing medical information DB in hub institutions for 10 million-scale data collection and establishing information analysis system within PMDA since 2011



Expected Outcomes：Prompt yet concise safety measures for medical products

①Comparing occurrences of adverse reactions

②Distinguishing between adverse reactions and disease symptoms

③Verification of the effectiveness of safety measures on reducing adverse reactions

Thank you for your attention