PMDA's Perspectives in Global Clinical Data Evaluation for Drug Approval

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Pharmaceuticals and Medical Devices Agency

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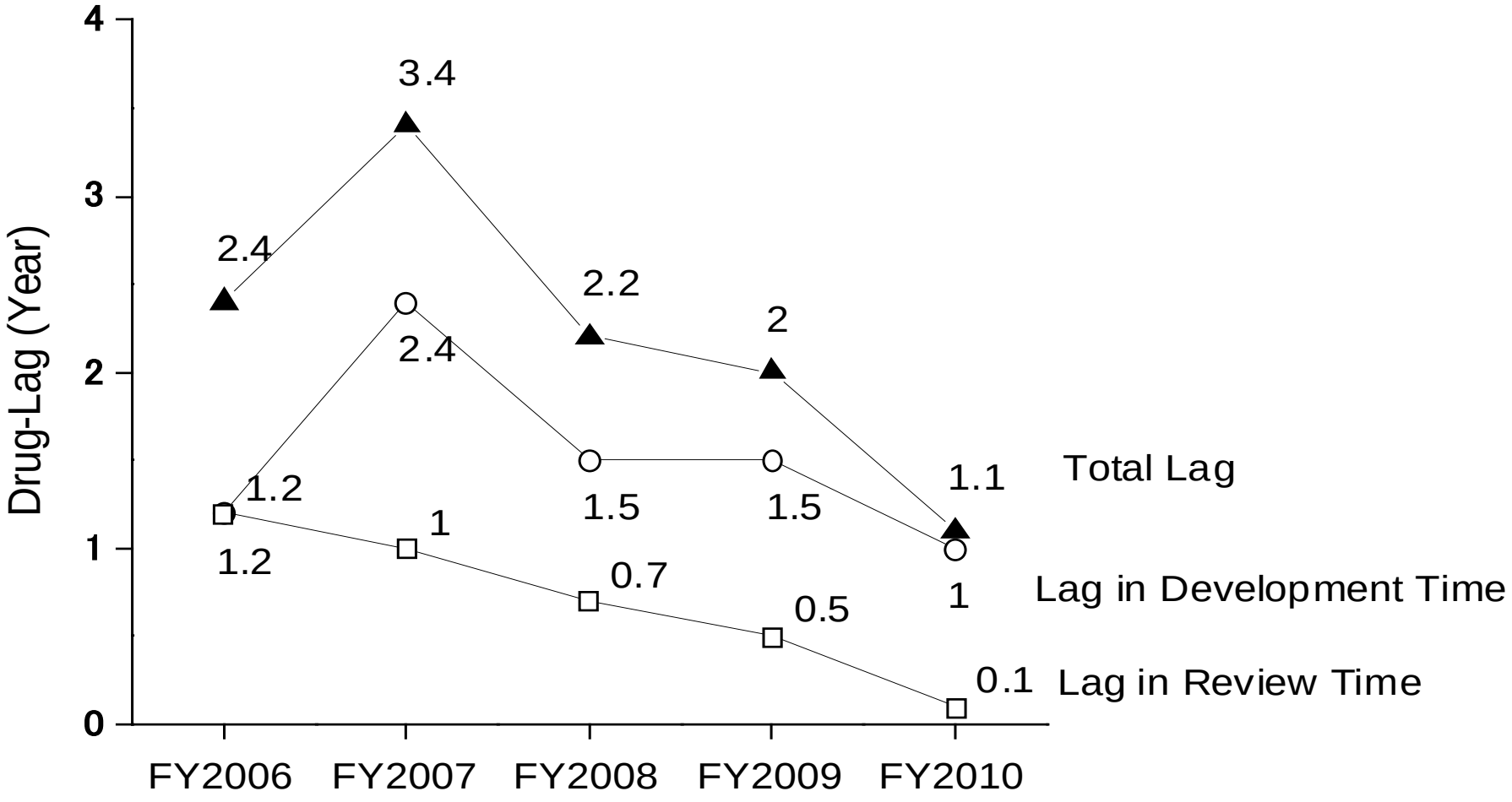
Recent trend of Dug-Lag in Japan



Basic principles on Global Clinical Trials

Japanese version

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用しているところである。

English version

September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evalution and Licecing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

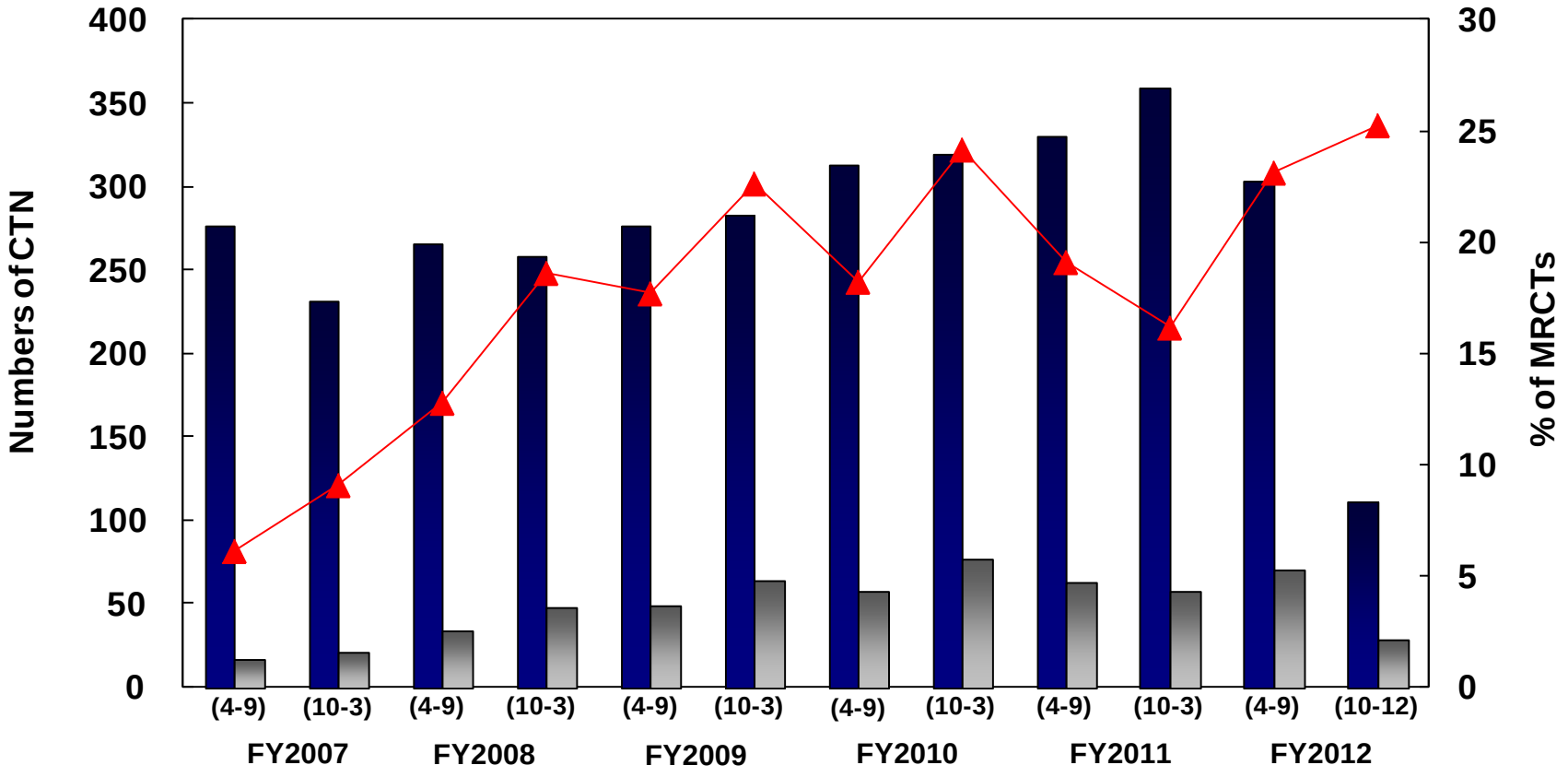
Basic principles on Global Clinical Trials*

Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called "Bridging" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

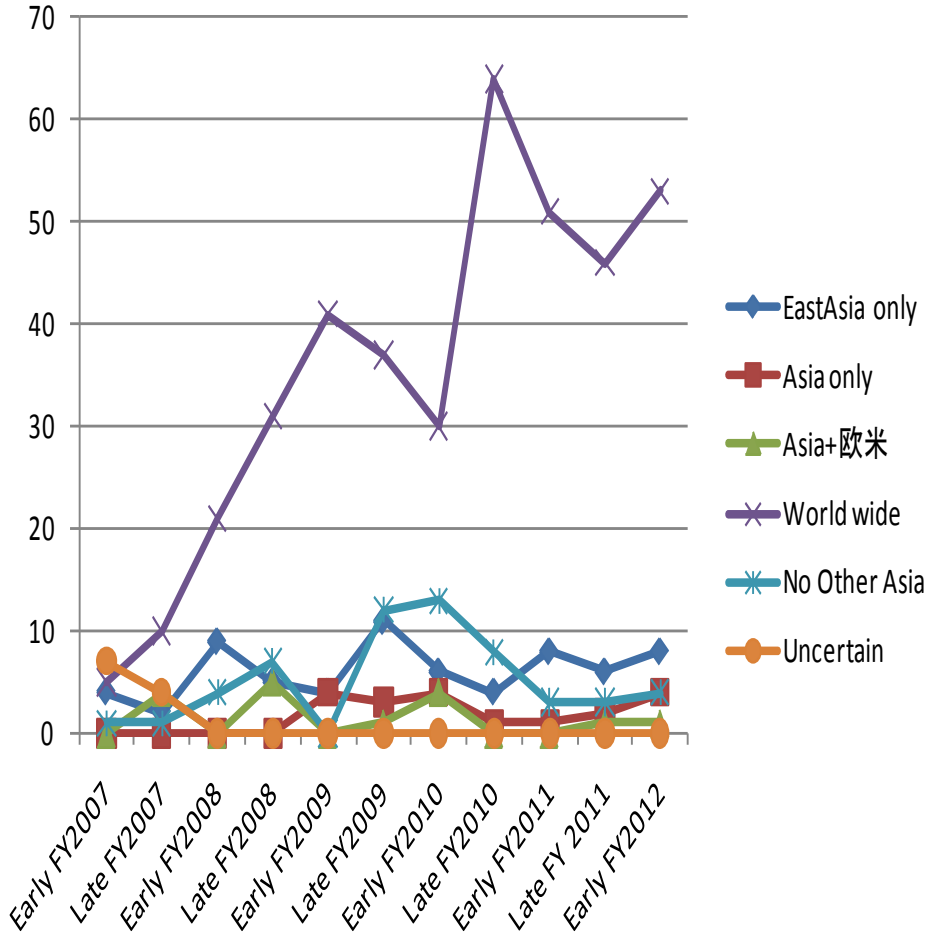
Japanese : http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf

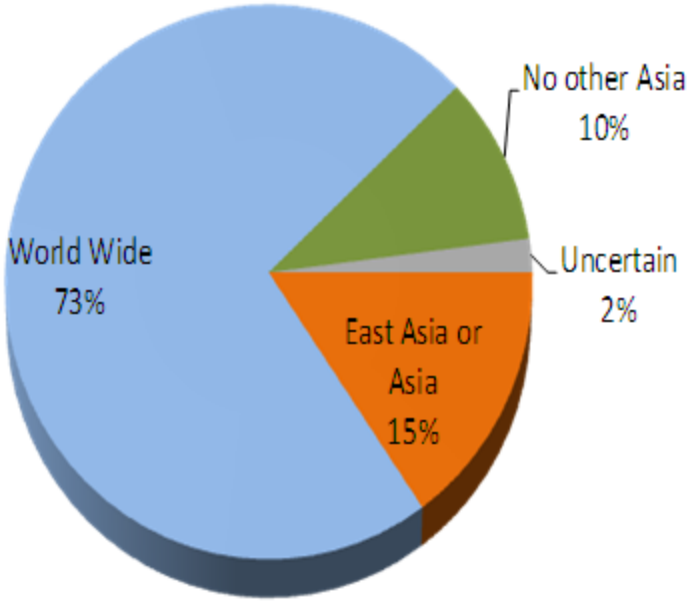
English : http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf

Trends of Global Clinical Trials including Japan

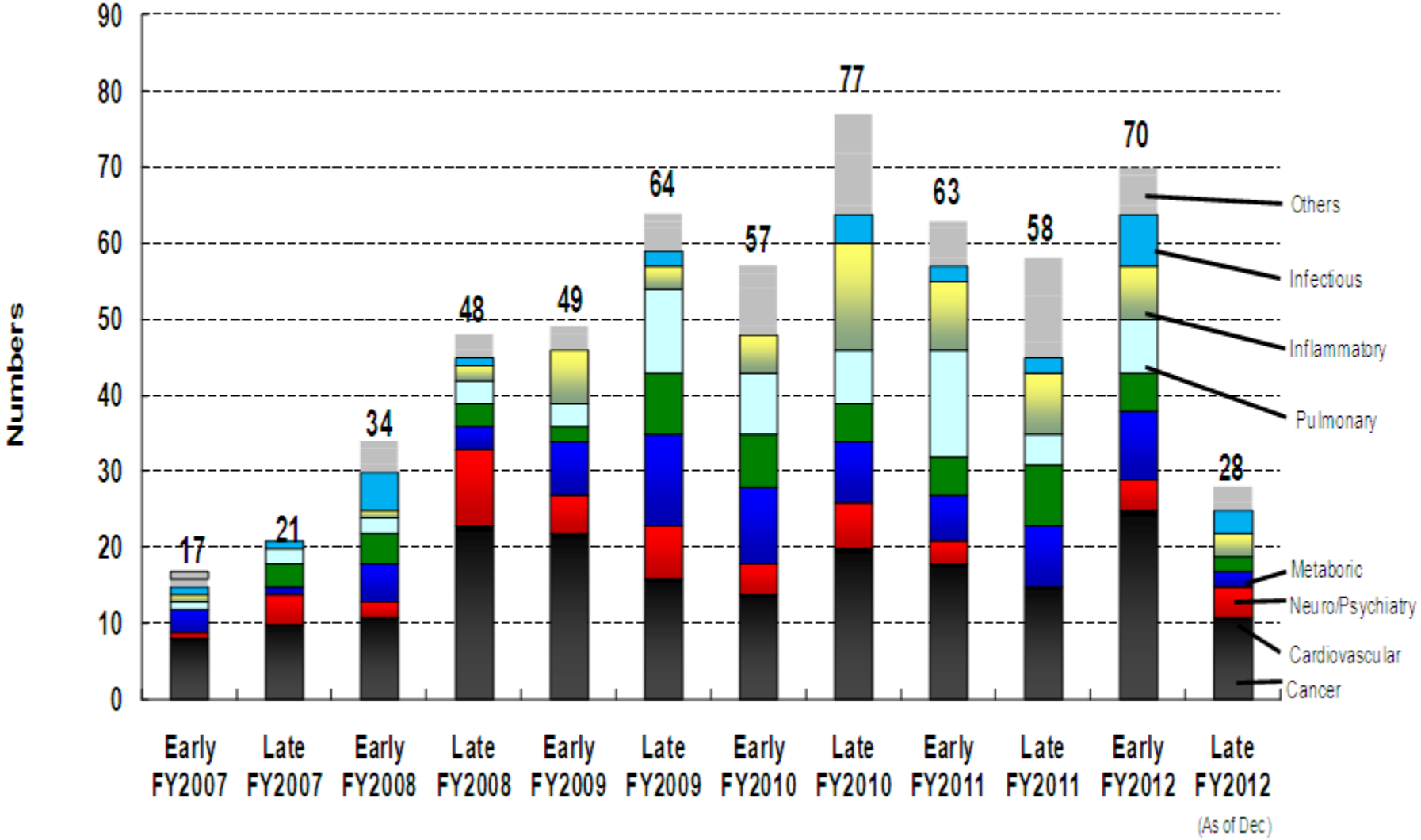


Operational Area of GCTs

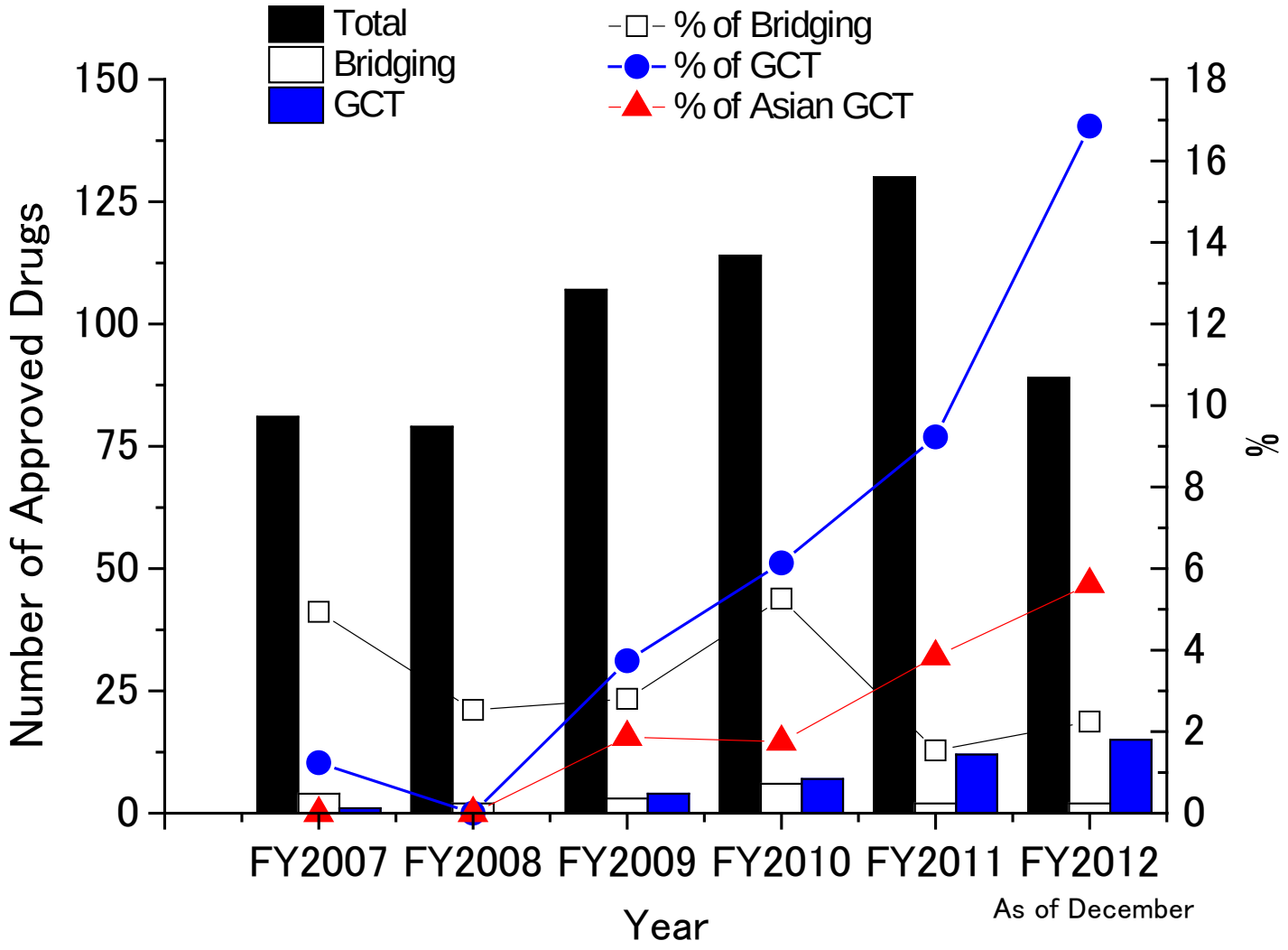




Target Disease of GCTs



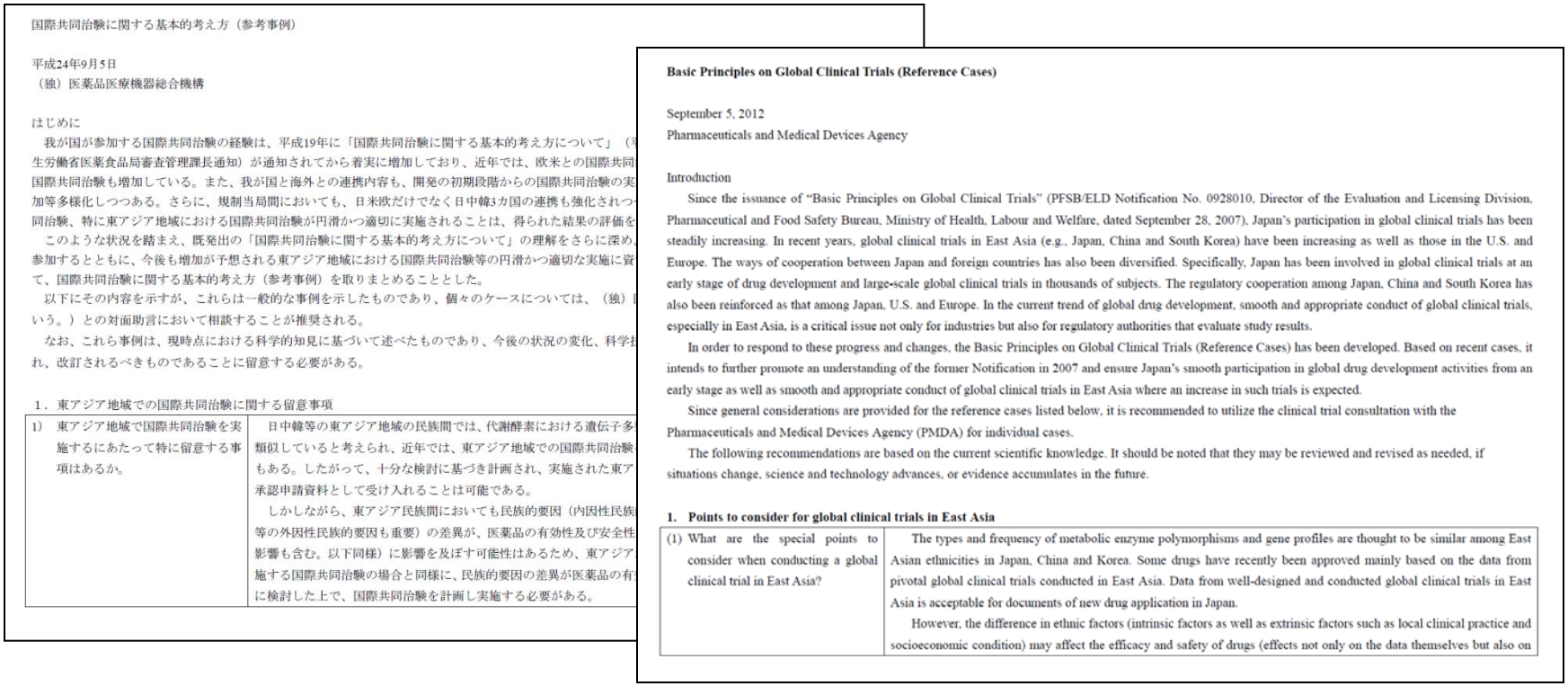
Development Strategy for drug approval in Japan



Asian GCT-based Drug approval in Japan

Name of Drug	Indication	Approval
Tolterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr. 2006
Insulin glulisine	Diabetes mellitus	Apr. 2009
Peramivir *	Type A and Type B Influenza virus infection	Jan. 2010
Temsirolimus	Advanced renal cell carcinoma	Jul. 2010
Laninamivir *	Type A and Type B Influenza virus infection	Sep. 2010
Edoxaban*	Prevention of venous thromboembolism after major orthopedic surgery	Apr. 2011
Indacaterol	Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.	Jul. 2011
Gefitinib	EGFR-Positive unresectable or metastatic non-small cell lung cancer (NSCLC)	Nov. 2011
Aripiprazole	Manic episodes associated with bipolar disorder	Jan. 2012
Exenatide	Type II diabetes mellitus (adjunctive to diet, exercise and treatment with SU)	Mar. 2012
Esomeprazol	Risk reduction of low-dose asprin-induced gastric or duodenal ulcer	Jun.2013
Stratera	Attention-Deficit/Hyperactivity Disorder in adulthood	Aug.2013
Insulin degludec*	Diabetes mellitus	Sep.2013
Insulin degludec/ Insulin aspart*	Diabetes mellitus	Dec.2013
Fesoterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Dec.2013

New Guidance (Sep 5th 2012): Basic principles on Global Clinical Trials *(Reference Cases)*



国際共同治験に関する基本的考え方（参考事例）

平成24年9月5日
（独）医薬品医療機器総合機構

はじめに

我が国が参加する国際共同治験の経験は、平成19年に「国際共同治験に関する基本的考え方について」（平
生労働省医薬食品局審査管理課長通知）が通知されてから着実に増加しており、近年では、欧米との国際共同
国際共同治験も増加している。また、我が国と海外との連携内容も、開発の初期段階からの国際共同治験の実
加等多様化しつつある。さらに、規制当局間においても、日米欧だけでなく日中韓3カ国の連携も強化されつ
同治験、特に東アジア地域における国際共同治験が円滑かつ適切に実施されることは、得られた結果の評価を

このような状況を踏まえ、既発出の「国際共同治験に関する基本的考え方について」の理解をさらに深め、
参加するとともに、今後も増加が予想される東アジア地域における国際共同治験等の円滑かつ適切な実施に資
て、国際共同治験に関する基本的考え方（参考事例）を取りまとめることとした。

以下にその内容を示すが、これらは一般的な事例を示したものであり、個々のケースについては、（独）
いう。）との対面助言において相談することが推奨される。

なお、これら事例は、現時点における科学的知見に基づいて述べたものであり、今後の状況の変化、科学
れ、改訂されるべきものであることに留意する必要がある。

1．東アジア地域での国際共同治験に関する留意事項

1） 東アジア地域で国際共同治験を実施するにあたって特に留意する事項はあるか。	日中韓等の東アジア地域の民族間では、代謝酵素における遺伝子多型類似していると考えられ、近年では、東アジア地域での国際共同治験もある。したがって、十分な検討に基づき計画され、実施された東ア承認申請資料として受け入れることは可能である。 しかしながら、東アジア民族間においても民族的要因（内因性民族等の外因性民族的要因も重要）の差異が、医薬品の有効性及び安全性影響も含む。以下同様）に影響を及ぼす可能性はあるため、東アジア施する国際共同治験の場合と同様に、民族的要因の差異が医薬品の有に検討した上で、国際共同治験を計画し実施する必要がある。

Basic Principles on Global Clinical Trials (Reference Cases)

September 5, 2012
Pharmaceuticals and Medical Devices Agency

Introduction

Since the issuance of "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007), Japan's participation in global clinical trials has been steadily increasing. In recent years, global clinical trials in East Asia (e.g., Japan, China and South Korea) have been increasing as well as those in the U.S. and Europe. The ways of cooperation between Japan and foreign countries has also been diversified. Specifically, Japan has been involved in global clinical trials at an early stage of drug development and large-scale global clinical trials in thousands of subjects. The regulatory cooperation among Japan, China and South Korea has also been reinforced as that among Japan, U.S. and Europe. In the current trend of global drug development, smooth and appropriate conduct of global clinical trials, especially in East Asia, is a critical issue not only for industries but also for regulatory authorities that evaluate study results.

In order to respond to these progress and changes, the Basic Principles on Global Clinical Trials (Reference Cases) has been developed. Based on recent cases, it intends to further promote an understanding of the former Notification in 2007 and ensure Japan's smooth participation in global drug development activities from an early stage as well as smooth and appropriate conduct of global clinical trials in East Asia where an increase in such trials is expected.

Since general considerations are provided for the reference cases listed below, it is recommended to utilize the clinical trial consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) for individual cases.

The following recommendations are based on the current scientific knowledge. It should be noted that they may be reviewed and revised as needed, if situations change, science and technology advances, or evidence accumulates in the future.

1. Points to consider for global clinical trials in East Asia

(1) What are the special points to consider when conducting a global clinical trial in East Asia?	The types and frequency of metabolic enzyme polymorphisms and gene profiles are thought to be similar among East Asian ethnicities in Japan, China and Korea. Some drugs have recently been approved mainly based on the data from pivotal global clinical trials conducted in East Asia. Data from well-designed and conducted global clinical trials in East Asia is acceptable for documents of new drug application in Japan. However, the difference in ethnic factors (intrinsic factors as well as extrinsic factors such as local clinical practice and socioeconomic condition) may affect the efficacy and safety of drugs (effects not only on the data themselves but also on

日本語：http://www.pmda.go.jp/regulatory/file/guideline/new_drug/GCT_jirei.pdf
英語：http://www.pmda.go.jp/regulatory/file/english_guideline/new_drug/GCT-jirei_en.pdf

Background of the New Guidance

- Accumulating new scientific knowledge and regulatory experiences after the publication of the 2007 guideline
- Diversifying a cooperation style between Japan and other countries; e.g. Asian GCT, Large-scale GCT
- Reinforcing the regulatory cooperation among Japan, China and South Korea as well as that among Japan, U.S. and Europe.

Further promotion of GCTs, especially in East-Asian region, is the key to successful drug development

Major points in the new guidance (Special points to consider in East-Asian GCTs: 1/2)

- Data from well-designed and conducted global clinical trials in East Asia is acceptable for new drug application in Japan.
- To conduct East Asia GCT appropriately and successfully, it is necessary to consider impacts on drug efficacy/safety of ethnic factor among East Asian populations before starting the trial
- Further accumulation and review of scientific data and information on East Asian populations will deepen our understanding of ethnic differences and ensure a smooth and appropriate conduct of global clinical trials in this region.
- It is encouraged to consider to include global clinical trials to be conducted in East Asia as part of drug development plan and accumulate information.

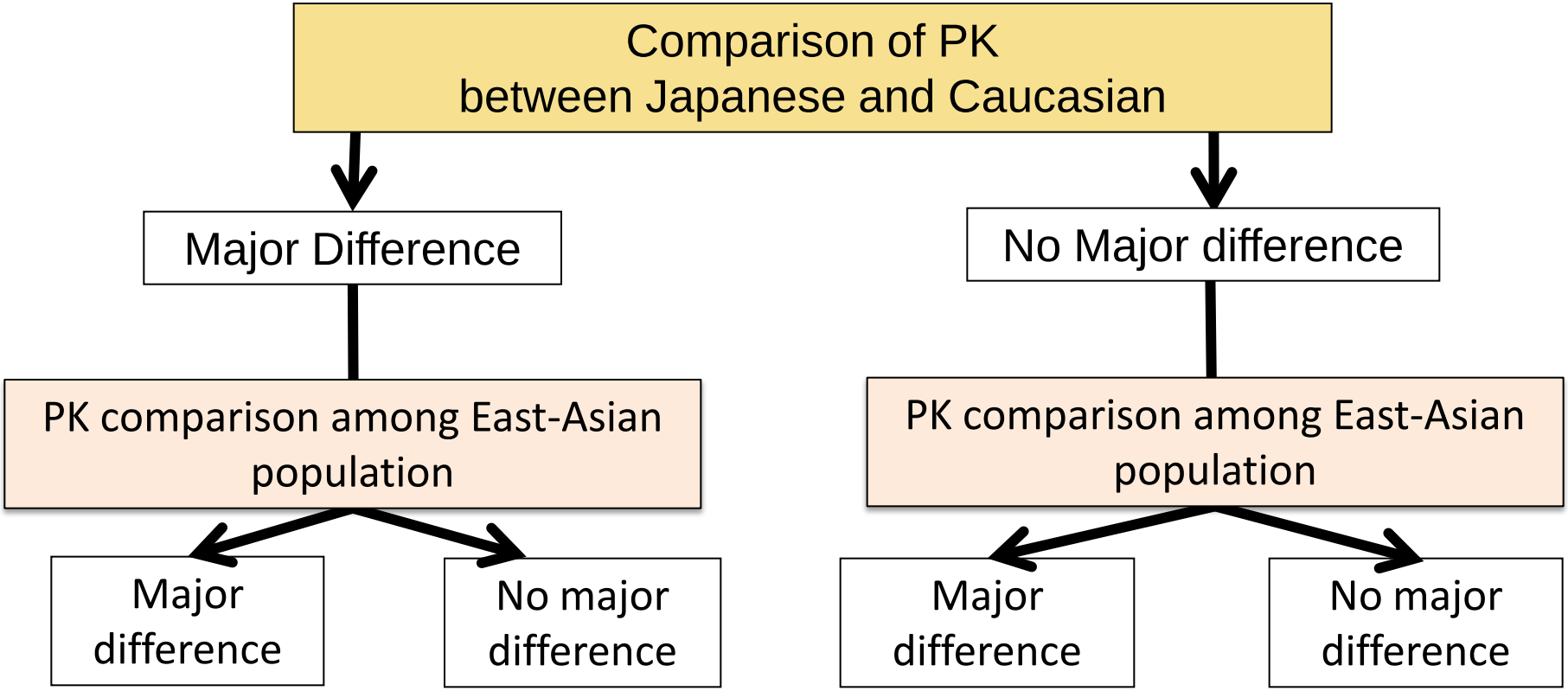
Major points in the new guidance (Special points to consider in East-Asian GCTs: 2/2)

- East-Asian GCT can be performed in any disease
- Proactive planning of East-Asian GCT is encouraged especially for diseases with high morbidity in East Asia (e.g., gastric cancer and hepatitis)
- Positioning of East-Asian GCT in entire global development plan should be clarified in advance
- All activities in East Asia should be carried out in cooperation with those in the U.S. and Europe.

Major points in the new guidance (Other points to consider)

- Daily cooperation with foreign partners (Affiliate, HQ, other regulatory agency etc.)
- Optimize a strategy based on collected data
- Acceptability of foreign population data on PK/PD
- Sample size calculation in case of large-scale GCT
- Safety assessment based on GCT, especially describing an importance of Japanese data on long-term safety evaluation

Classification of development strategies based on PK-profile



Local study in Japan

Regional study in East Asia

Collaboration study in Japan/US/EU

World wide collaboration

Future GCTs

Challenges for better GCTs

- Effects of ethnic factors on drug efficacy/safety should be more characterized
- Methods for planning/evaluation should be established
  - Sample size calculation, consistency evaluation etc.
- Regulatory harmonization

Advancing regulatory science

Regulatory Science Research

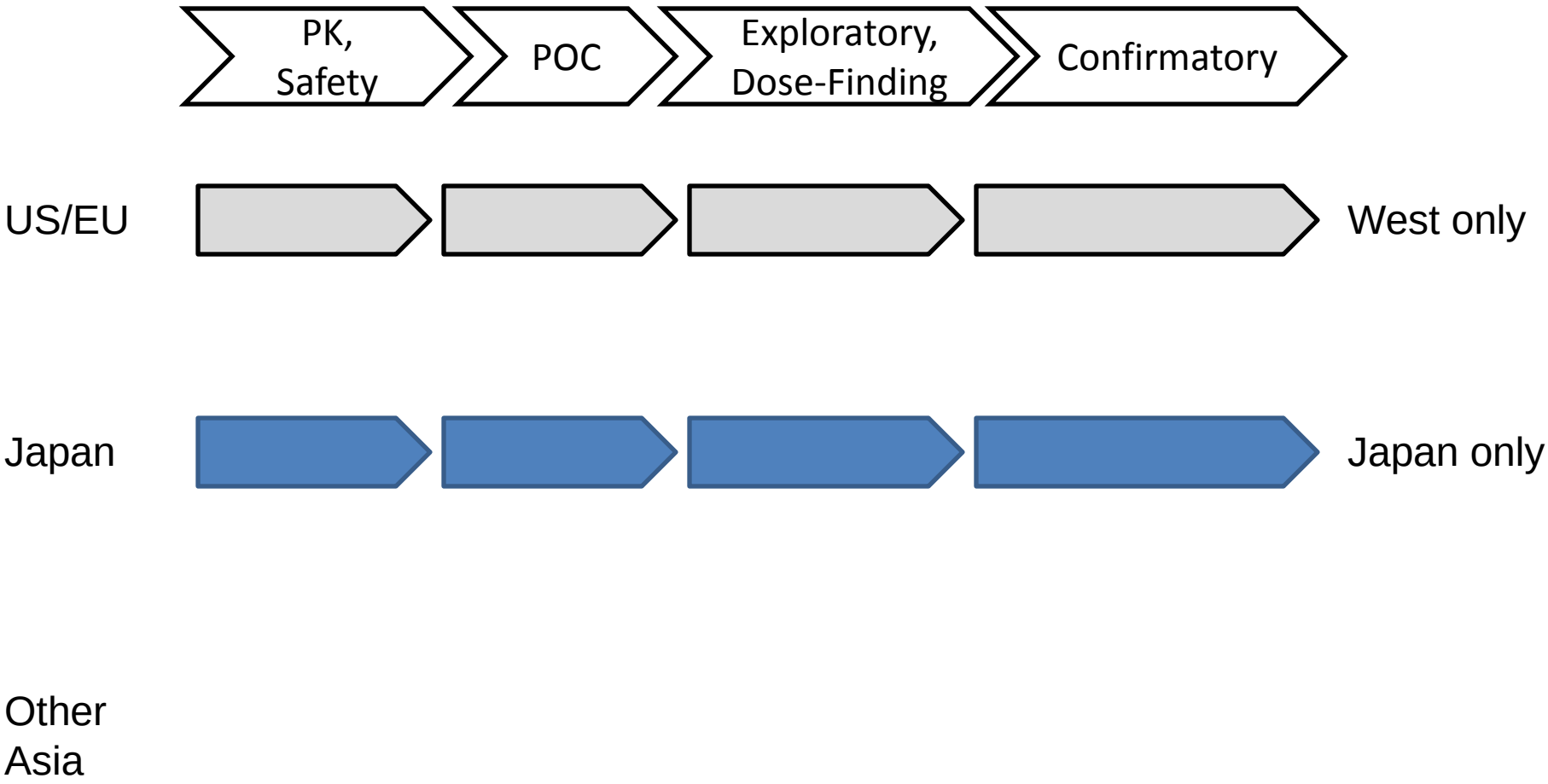
- China/Korea/Japan Tripartite Working Group
- MHLW Research group

  (Kawai study group, Saito study group)

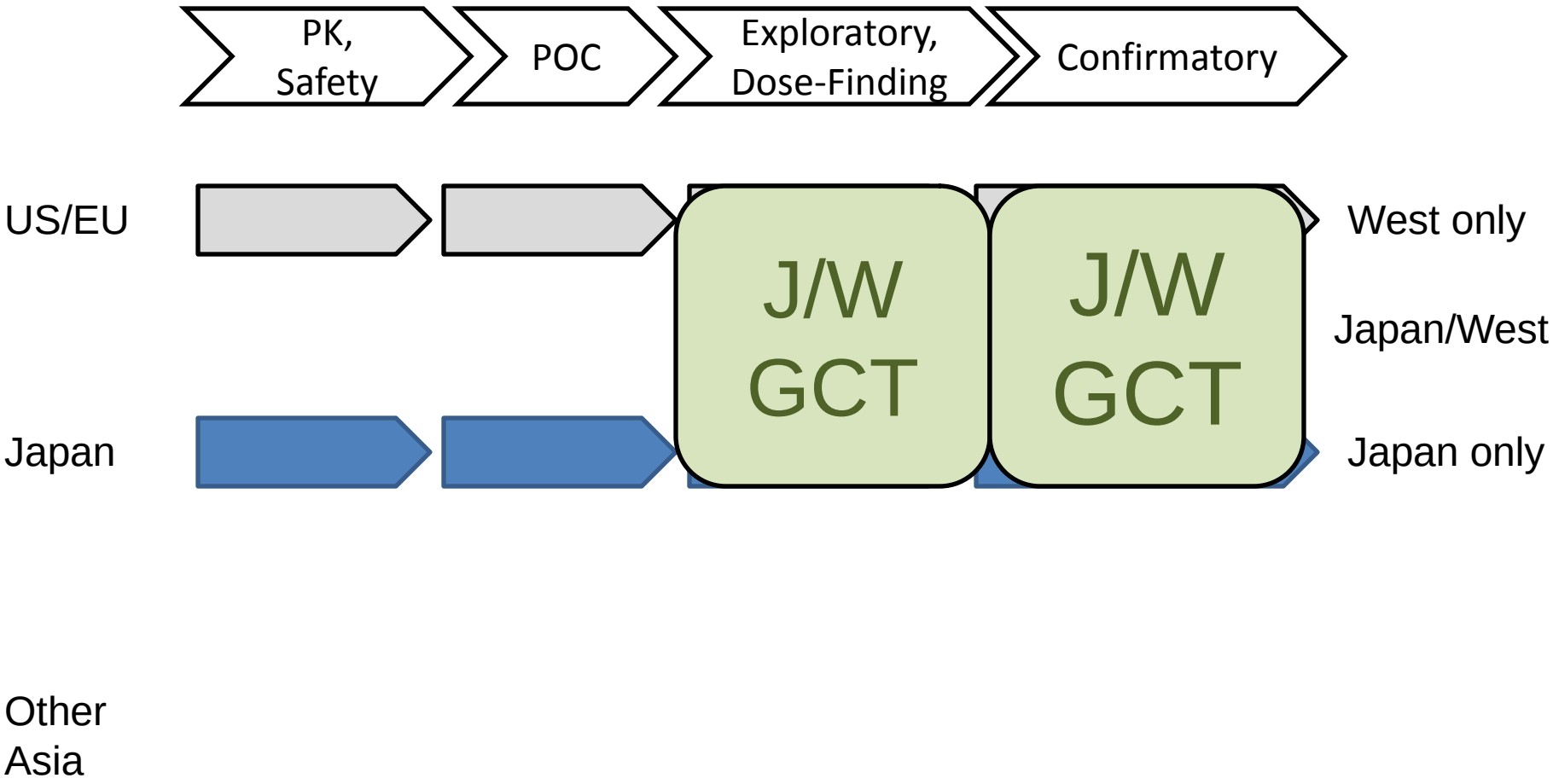
  – Examining impacts of ethnic factor on drug efficacy/safety

  – Clarifying points to consider in better planning and data evaluation of GCTs

Development Strategy



Development Strategy



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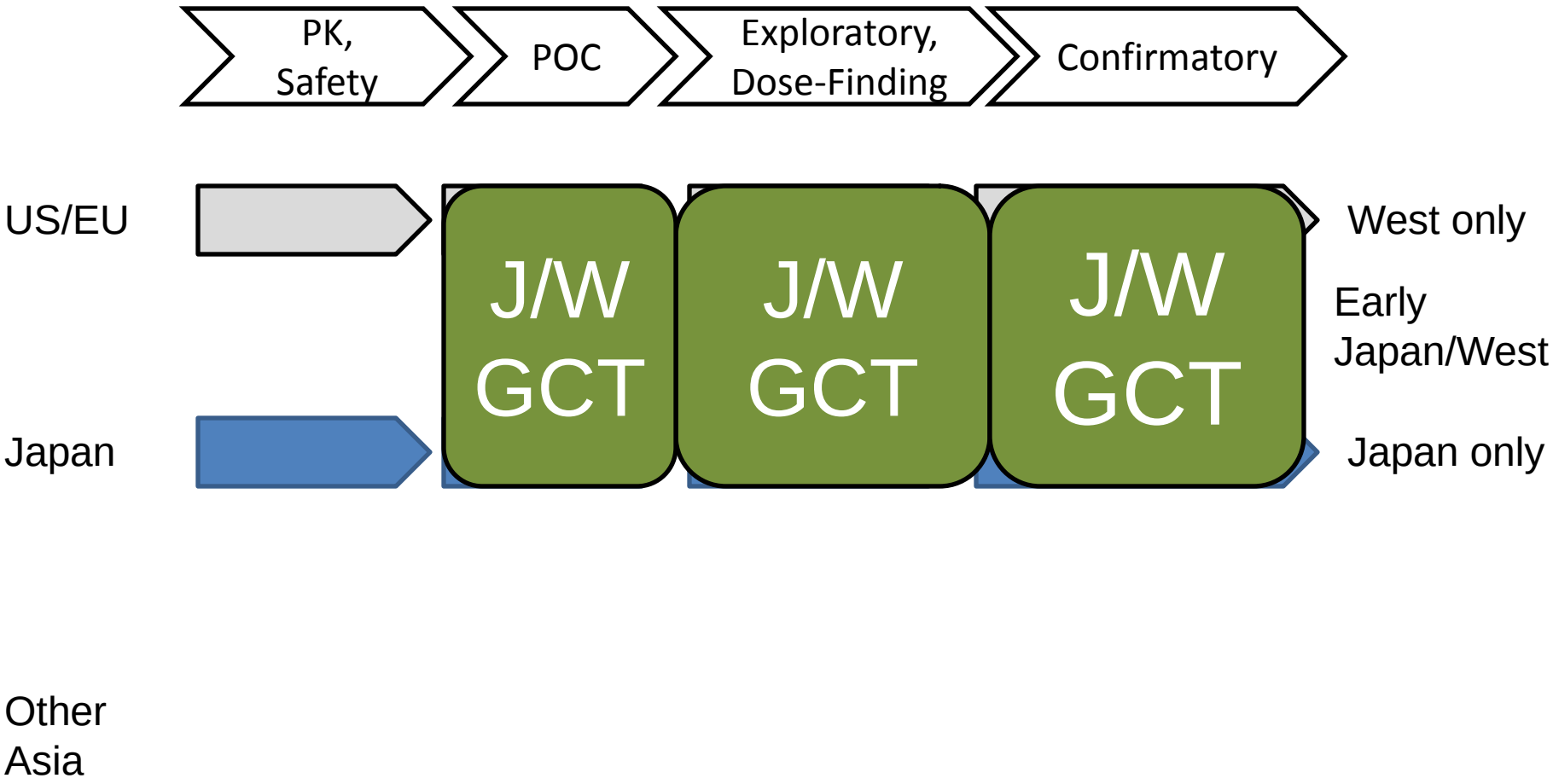
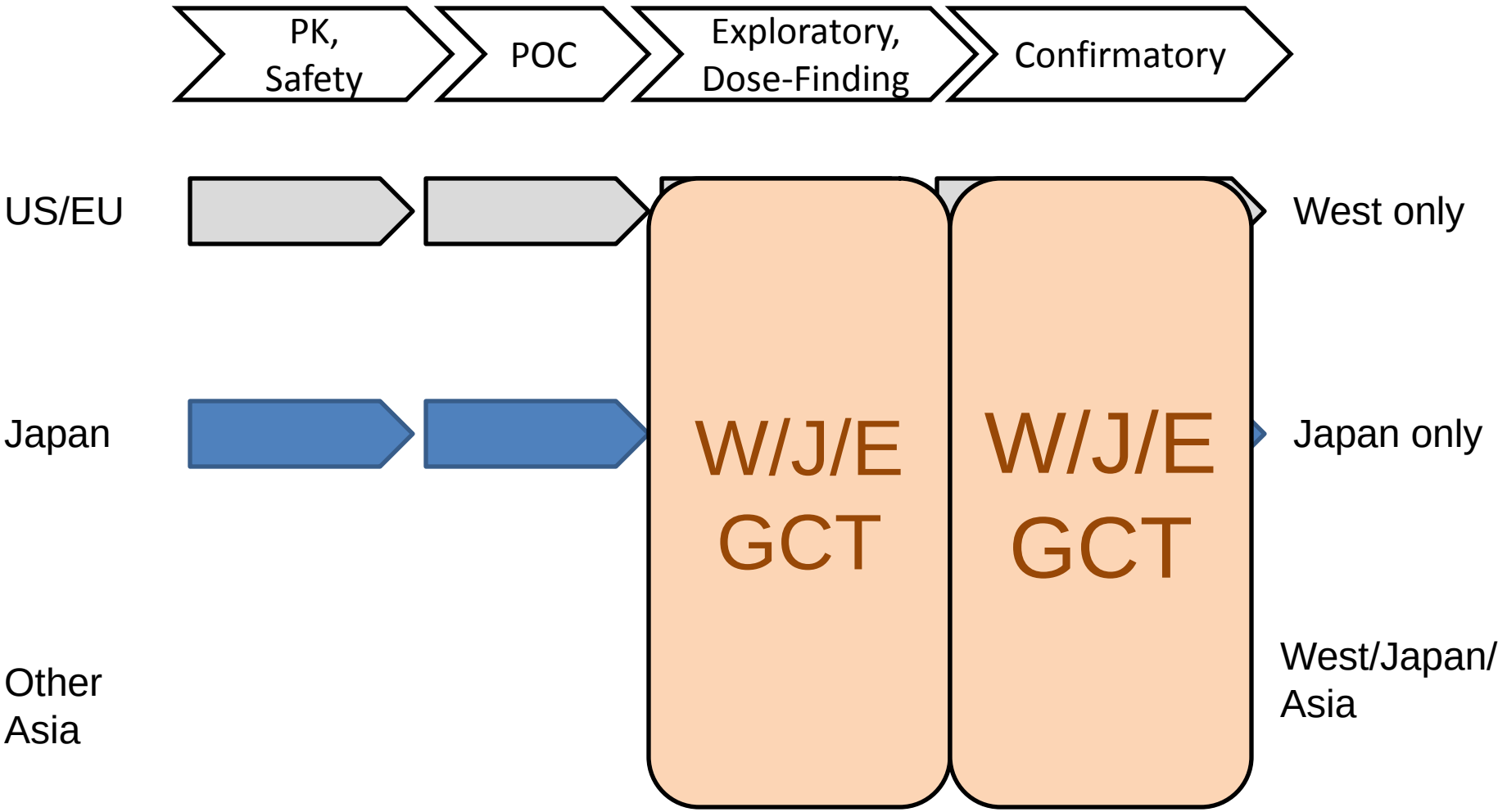
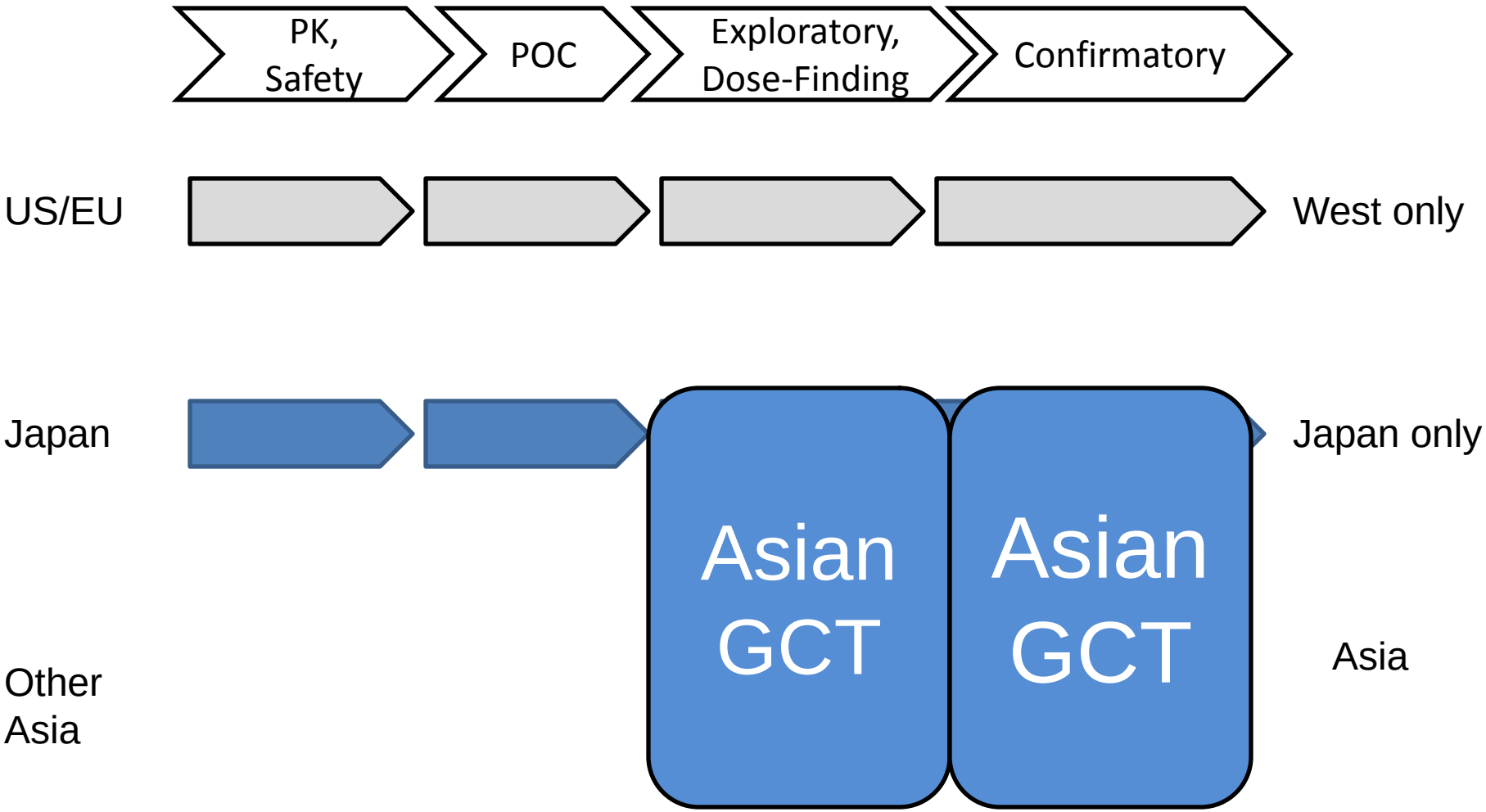


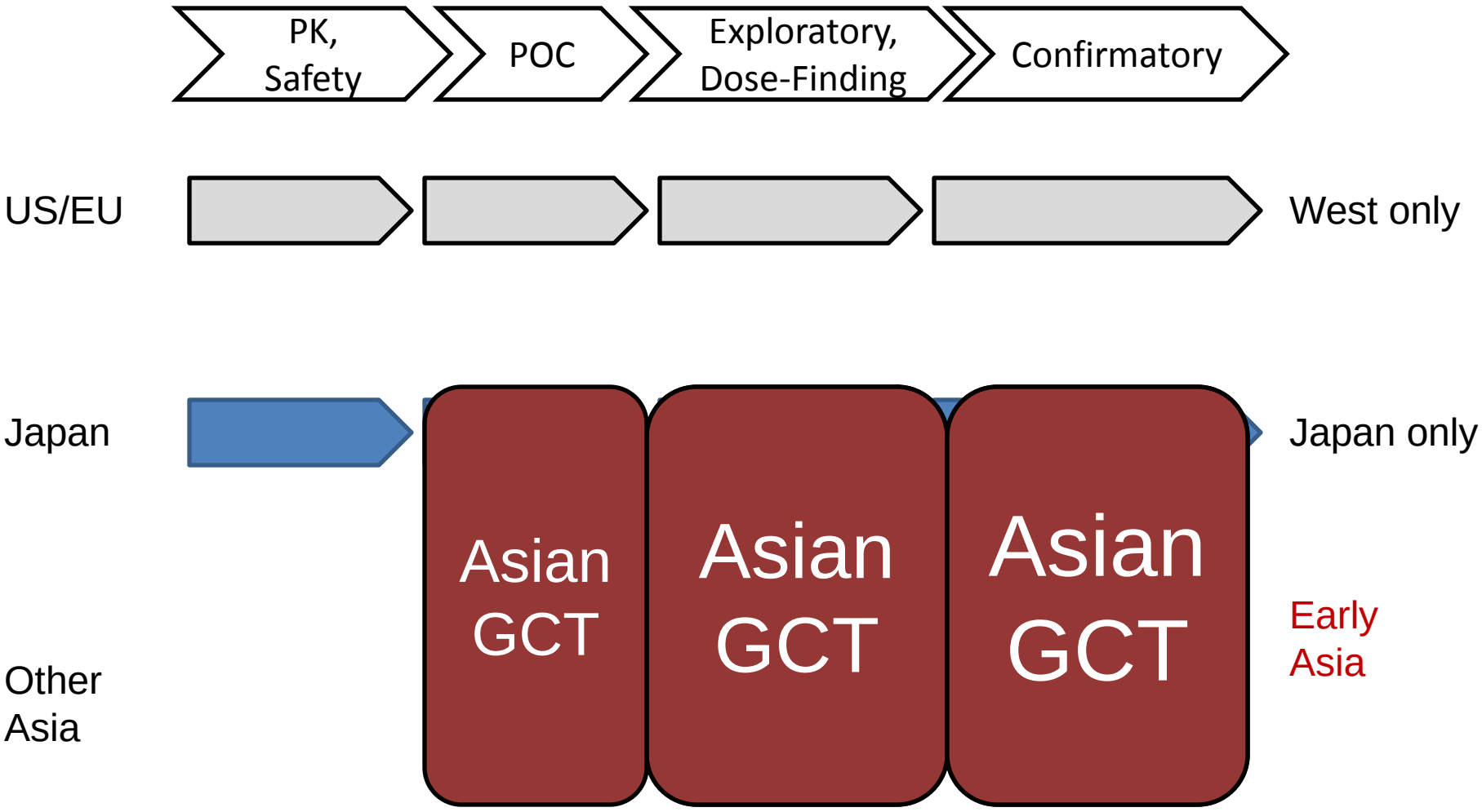
Development Strategy



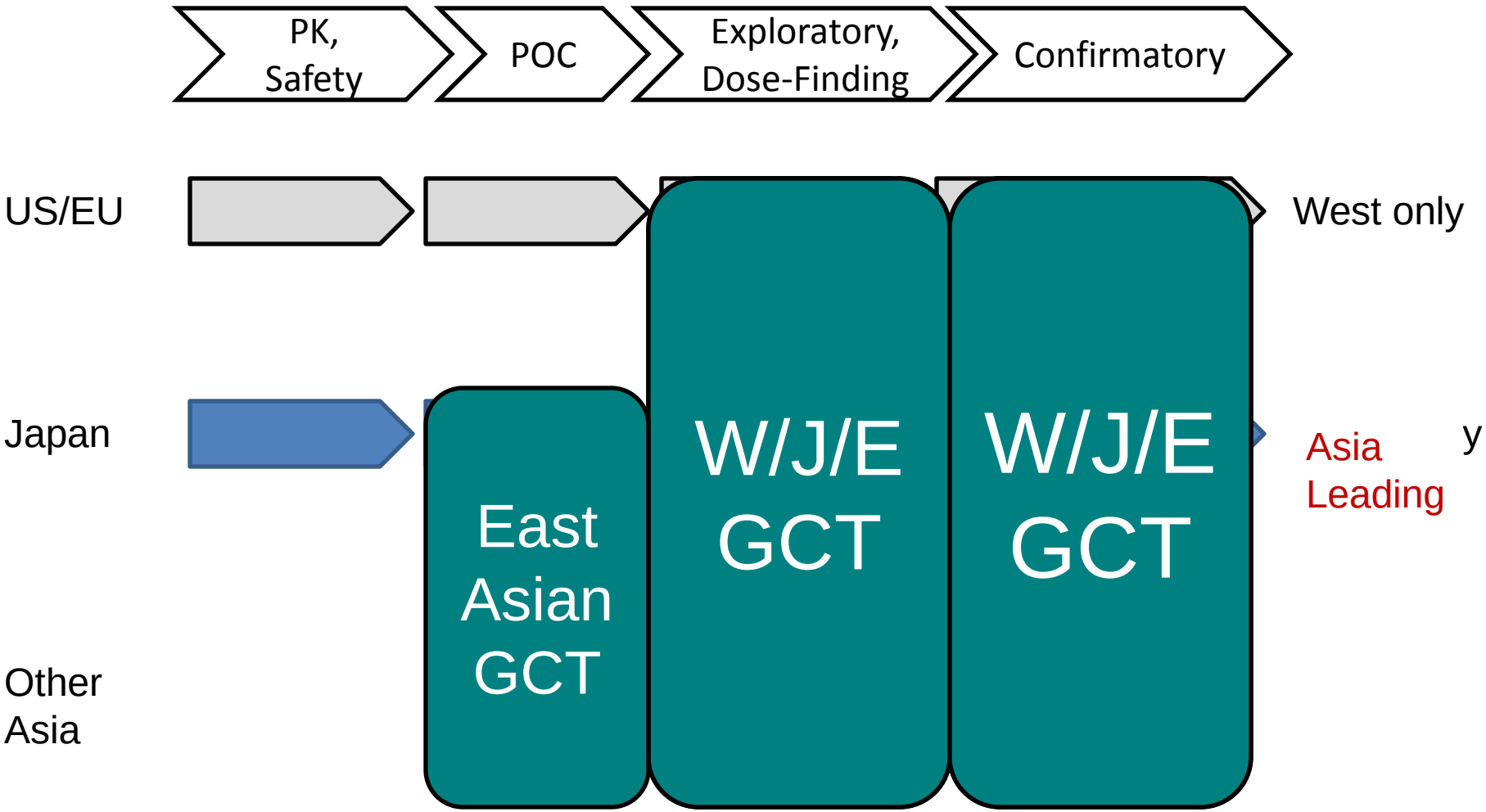
Development Strategy



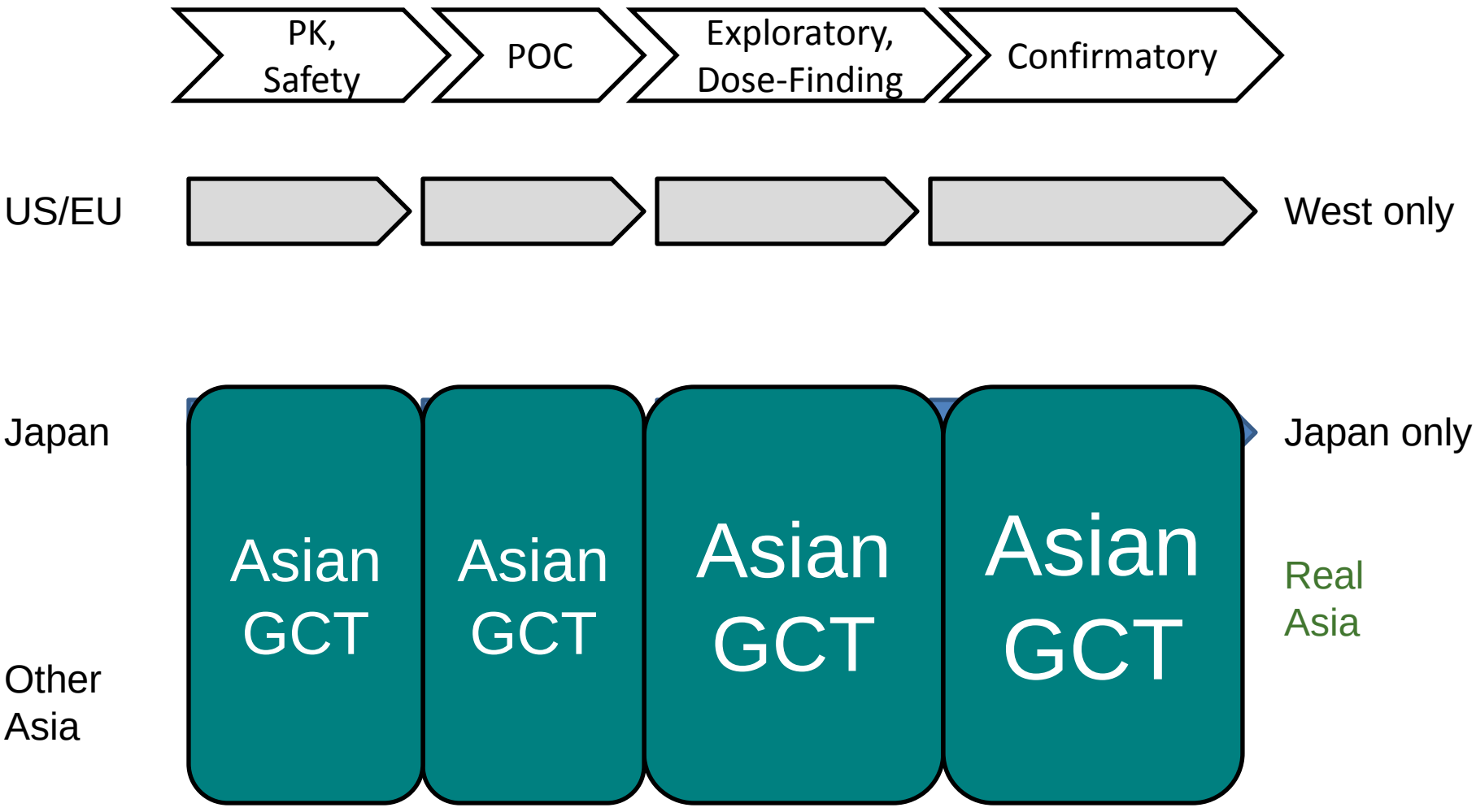
Development Strategy



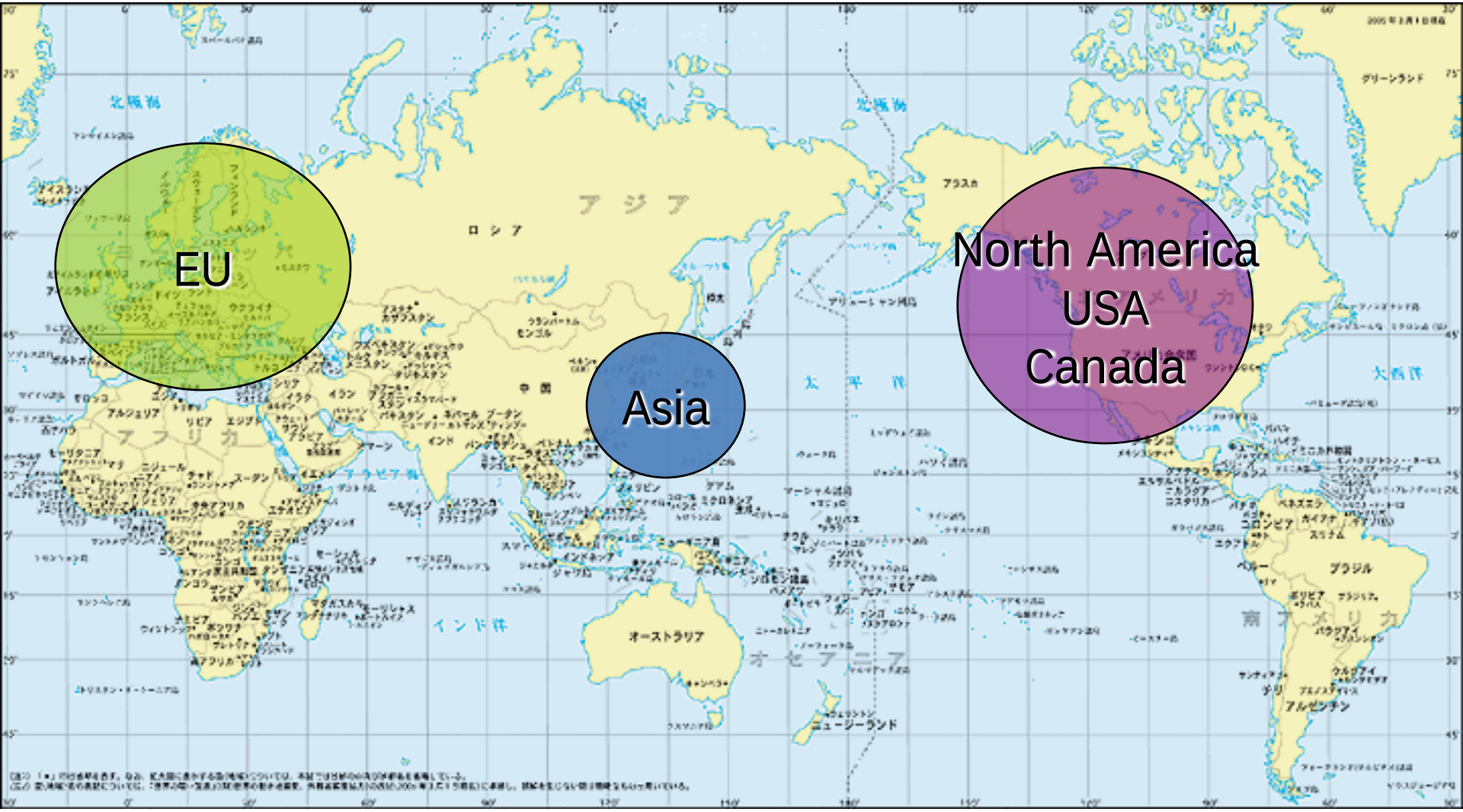
Development Strategy



Development Strategy



Drugs from Asia to the world



Cooperation for better drug developments

Information

- HOMEPAGE (English)
  http://www.pmda.go.jp/english/index.html
- Regulatory Science Page
  http://www.pmda.go.jp/regulatory/index.html
- E-mail:
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention