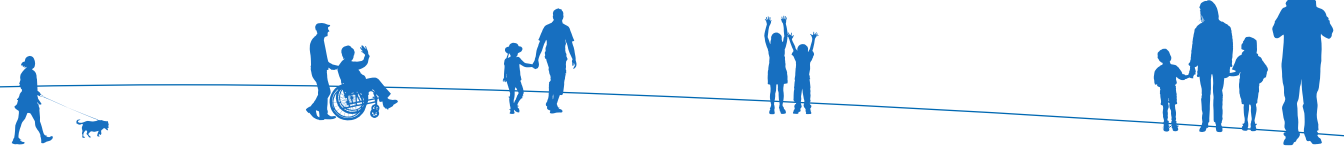
PMDA

Making everyone's lives brighter together

Why Japan

for drug development Vol.2



Japan: What is attracting?

Large Market

-The world's 3rd largest pharma market

Flexibility/ Predictability

-Review
: fastest in the world
-Reimbursement
: prompt decisions
-Consultation
: available from an early stage of development

Advantages

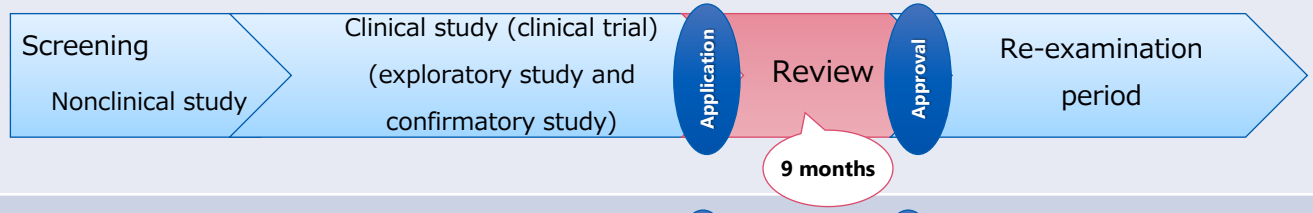
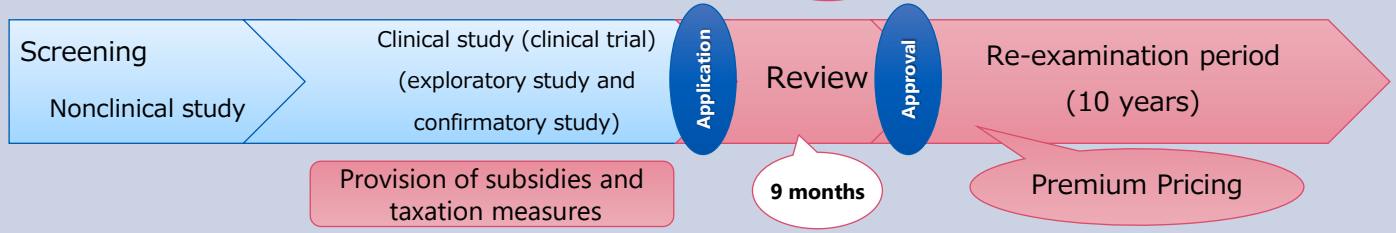
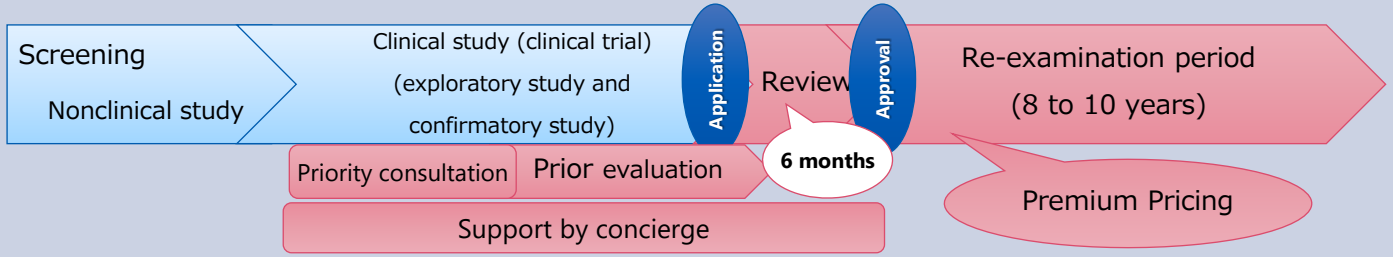
-Designation
: additional support based on product characteristics

Further merit

-Regulation: Development
: Orphans
: Amendment of PMD Act

PMDA

Accelerated Review Systems on Pharmaceuticals in Japan

System name and designation requirements	Outline
Standard review	
Priority review (1) The disease is serious. (2) The efficacy or safety is much better than that of existing treatments.	
Orphan drug * In addition to priority review, (1) less than 50,000 patients or designated intractable diseases (2) the development possibility	
Conditional approval system for drug * In addition to priority review, (1) it is difficult to conduct the confirmatory study (2) certain efficacy and safety were confirmed in other studies	
Innovative drug, "Sakigake" (1) Innovativeness (2) For serious diseases (3) Prominent efficacy (4) Being applied in Japan for the first time in the world	

When overseas clinical development has already started ahead of Japan, do we still need clinical trials in Japan?

Case 1: Japanese Phase 1 Trial before Initiating Multi-Regional Clinical Trials

Case 2: Basic Principles on Japanese Data when Pivotal Trials are Conducted Only Overseas

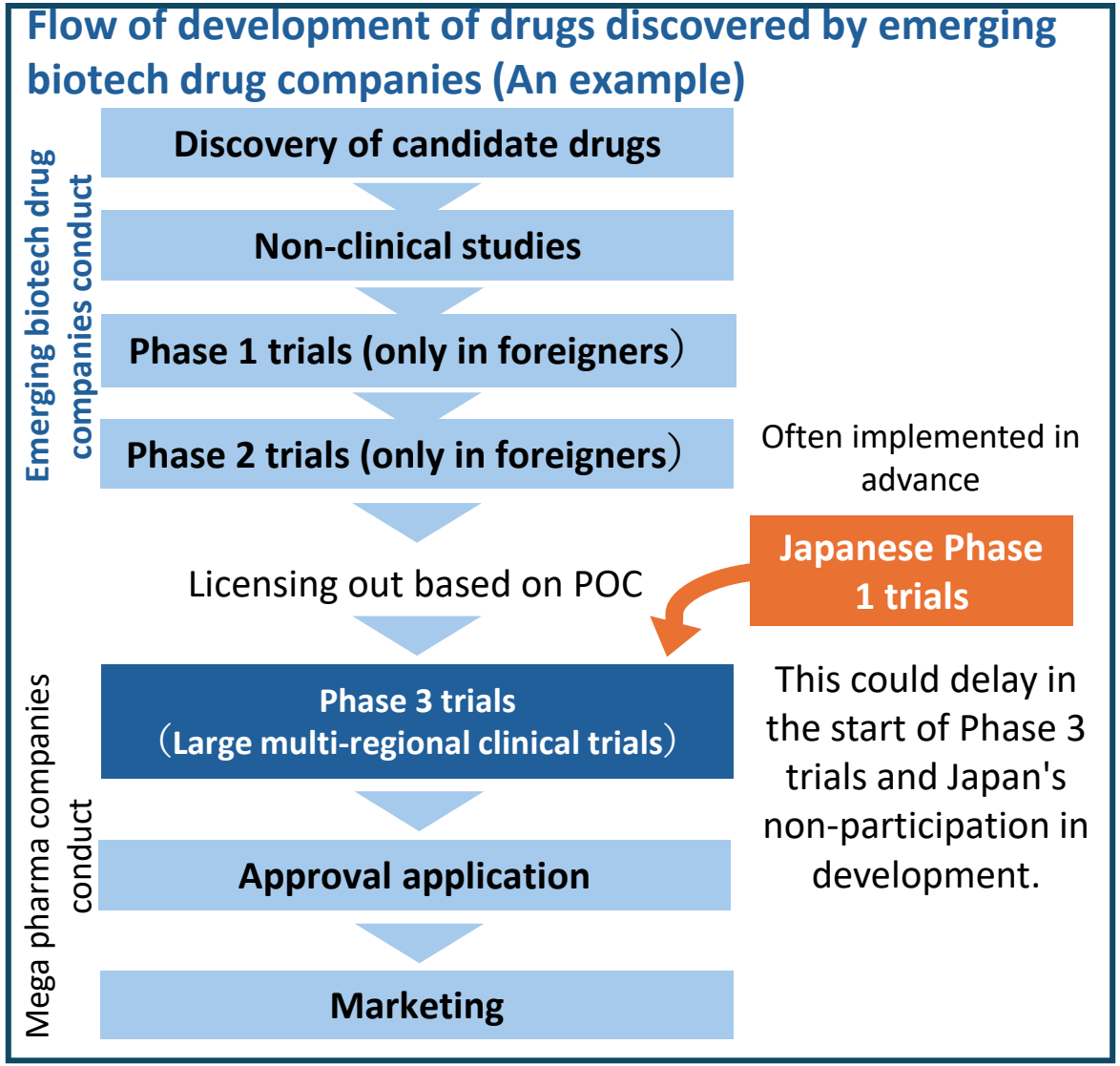
Necessity of Japanese Phase 1 Trial before Initiating Multi-Regional Clinical Trials for Drugs in which development is preceding outside Japan

[Backgrounds]

- When Japan participates in multi-regional clinical trials, if the explanation on safety in Japanese is insufficient, it is necessary to conduct Phase 1 trials in Japanese.
- Because it takes certain time and cost to conduct Phase 1 trials in Japanese, it is noted that development in Japan is abandoned in order to avoid delay in the start of Phase 3 trials.

[PMDA's principle]

- If there are ethnic differences between Japanese and foreigners, we recognize that the Japanese data are important in using drugs safely in Japan
- From the previous, we <u>have not uniformly required</u> Phase 1 trials in Japanese before participating in multi-regional clinical trials, and determines <u>synthetically by considering multiple perspectives</u>.
- It is desirable that Japan participates in multi-regional clinical trials from early stage in development and Japanese data are collected.



(only in Japanese) https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html

Basic Principles for Conducting Phase 1 Studies in Japanese prior to Initiating Multi-Regional Clinical Trials including Japan for Drugs in which Early Clinical Development is Preceding outside Japan•Q&A

PSB/PED Notification No. 1225-2, dated December 25, 2023, by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau of MHLW
Administrative notice, dated December 25, 2023, by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau of MHLW（Q&A）

It is stated that in principle, an additional phase 1 trial in Japanese is not needed, if the safety and tolerability in Japanese participants can be explained and the safety is clinically acceptable and manageable based on the available data.

Ministry of Health, Labour and Welfare

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Q&A for basic principles for conducting
initiating multi-regional clinical trials incl
clinical development is pr

Notification

Q&A

https://www.pmda.go.jp/english/review-services/regulatory-info/0013.html

Cases where participation of Japanese patients in MRCT without Phase 1 trials with Japanese participants are acceptable

High unmet medical needs

In case where

- Drug addresses high unmet medical needs and
- Participation in planned or ongoing MRCTs is desirable
  - drugs for rare diseases,
  - diseases that are refractory and serious,
  - or pediatrics

Safety of Japanese participants is manageable

In case that

- safety of Japanese participants is clinically acceptable and manageable

Points to consider when evaluating safety of Japanese participants

- Consider “the safety of investigational drug” and “the impact of ethnic factor associated with investigational drug” together

  - consider comprehensively based on non-clinical data, results of clinical trials already initiated overseas, available knowledge including information on similar drugs, modeling and simulations etc.

- Consider the possibility of the risk to Japanese participants in the MRCTs becomes greater than the risk to non-Japanese participants

Judge whether the safety of the dosage to be evaluated in the MRCTs of the Japanese participants are clinically acceptable/manageable

Q&A

Points to consider when considering the necessity of Phase 1 trial with Japanese participants before the initiation of MRCT

- For example, the necessity of Japanese Phase 1 trials should be judged more carefully if (a) the drug is expected to cause serious adverse events frequently and has a narrow safety margin, such as in anti-cancer drugs, and (b) safety data is limited because of no experience of administration in Japanese

- Even if the Japanese Phase 1 trial was not conducted, it is important to assess the differences in PK and/or PD between Japanese and non-Japanese, by measures such as collecting PK/PD data in the MRCTs.

- Concerning the necessity of Japanese Phase 1 trials and appropriateness of MRCT safety measures, judgement should be made for each individual drug, thus, please do consult with PMDA.

Basic Principles on Japanese Data when Pivotal Trials are Conducted Only Overseas

Ministry of Health, Labour and Welfare

PMSB/ELD Notification No. 1023-3, dated October, 23, 2024, by Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau of MHLW

Basic Principles on Japanese Clinical Trial Data for Drugs for Rare Diseases, etc., for Which Confirmatory Clinical Trials Have Been Conducted Only Overseas

(1) If drugs meet all of the case 1 to 3, it is possible to submit an application for approval without clinical trial data in Japanese patients

1. The pivotal trial has already been appropriately conducted overseas

2. Conducting additional clinical trials are impracticable due to a very small number of patients or other factors

3. The benefits for Japanese patients are expected to outweigh the risks based on comprehensive consideration with the obtained information on efficacy and safety

(2) However, if there is specific evidence indicating that there are clinically meaningful ethnic differences between non-Japanese and Japanese patients based on the characteristics of the drug or the data of similar drugs, and it is determined that additional information regarding the safety and appropriate dosage is needed, clinical trials (including clinical pharmacology studies) in the Japanese population may be deemed necessary.

difficult, whether it is possible to apply data from foreign populations to the Japanese population have been comprehensively examined based on detailed medical information on individual participants.

* This English version of the Japanese Notification is provided for referenc
event of any inconsistency between the Japanese original and the English translation, the former shall

https://www.pmda.go.jp/files/000275134.pdf

Early Consideration

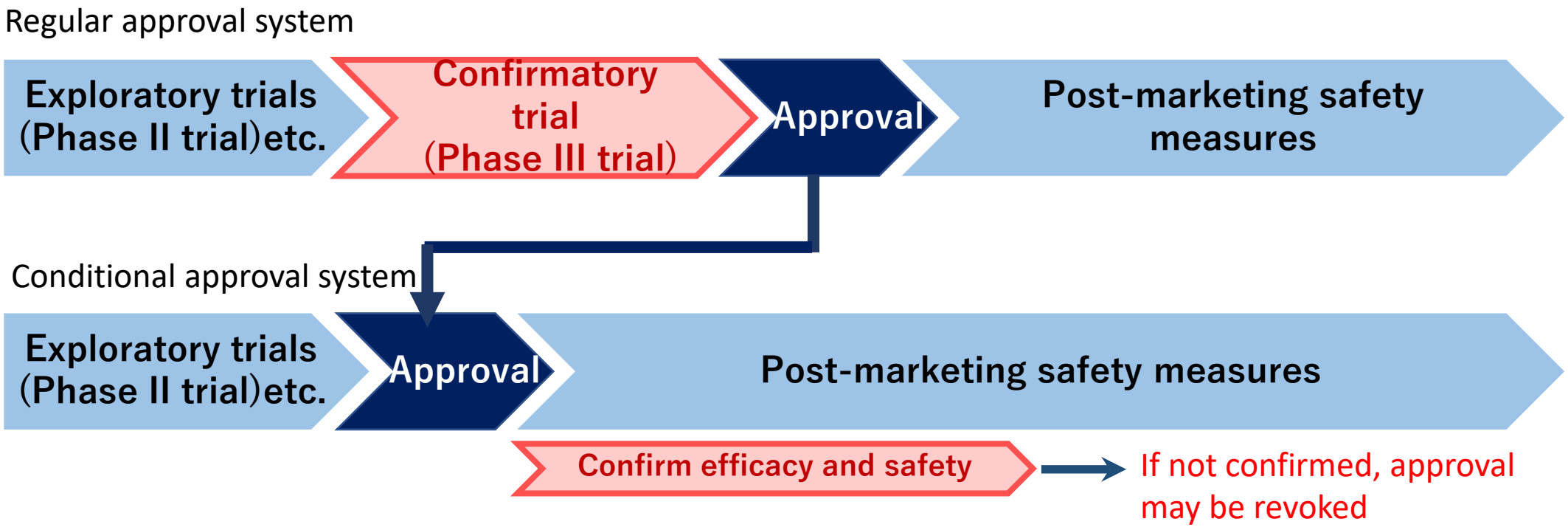
- ***Early Consideration is reference information and point of view at that time*** *for promoting the practical application of new technologies and other innovations and the development of innovative pharmaceuticals, etc.,* ***although scientific knowledge and information have not yet been fully accumulated****.*

Recent Early Consideration

- ☐ Points to consider for externally controlled trials
- ☐ Points to consider for nonclinical safety matters when submitting the initial clinical trial notification
- ☐ Points to consider for the discussion with PMDA using the ICH S1B (R1) guideline and in the approval application
- ☐ Points to consider in developing drugs for pediatric inflammatory bowel disease
- ☐ Points to Consider for Clinical Efficacy Evaluation of Drugs for Palmoplantar Pustulosis

https://www.pmda.go.jp/english/review-services/regulatory-info/0005.html

Conditional approval system after revision (image)



Scope of the system

- When clinical efficacy is reasonably foreseeable based on the results of exploratory trials etc.
- When there is a high unmet medical need due to reasons such as the disease is serious and has no other adequate alternative treatment

Conditions for approval

- After approval, in principle, efficacy and safety should be ensured by conducting a confirmatory trial.
- When necessary, requirements should be set out with regard to medical institutions, physicians, etc. who use drugs.
- Information obtained after approval and its evaluation need to be disclosed.

Towards the amendment act

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act)

1. **Revision to the conditional approval system of the drugs etc. for rare and/or serious diseases**

   The **conditional approval system** for pharmaceuticals, medical devices or in vitro diagnostics with high medical needs, such as when there is no appropriate alternative and serious treatment, should be reviewed to allow approval when clinical usefulness can reasonably be expected during the **exploratory phase**, with provisions for withdrawal of approval.

2. Promotion of making a pediatric drugs development plan

   Applicants for adult drugs should be obliged to **make efforts to plan the development of pediatric drugs**. In addition, the **maximum reexamination period should be raised to 12 years** (the reexamination period can be extended to the development of pediatric drugs for which the reexamination period has been set at 10 years).

Activities for Enhancement of Cooperation with the US

- For development and introduction of innovative drugs or medical devices in Japan, we provide locally (at sales meeting, academic society, etc.)
  - ✓ Information dissemination to each US start-up companies in English
  - ✓ Early development consultation (providing free regulatory consultations in English)
- Enhancement of regulatory cooperation locally between PMDA and FDA and exchange of information on regulation

Items invited for development at “Study Group on Unapproved and Off-label Drugs”

Development and regulatory application in Japan

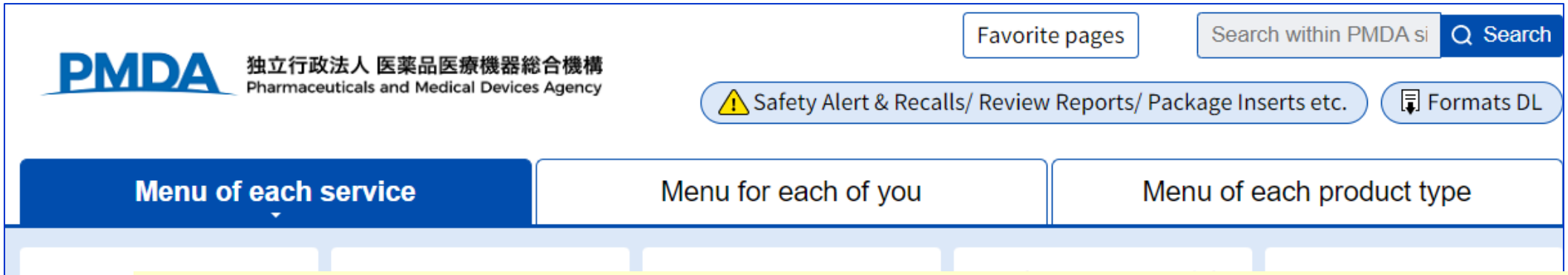
Washington D.C. Office

They can consult us with English materials (Japanese translation will not be required)

Aiming at development and approval in Japan

Cited from MHLW “Main matters on the budget proposal” in 2024

Overview of consultation services at Washington D.C. Office



Overview of the general consultation

- Scope of consultations
  - ✓ Exchange of views with regard to general questions and concerns about regulations and other related notices
  - ✓ Details, flows and scope of RS strategy consultation service
- Free-of-charge (no record of consultation will be made)
- This consultation service is available in English (30 min. /session)
- Service hours: from 10.00 a.m. to 5.00 p.m. (EST)
- Either face-to-face or online
- Related governmental organizations such as JETRO may cooperate in the consultation (on a case-by-case basis)

1. Scope of Consultation

https://www.pmda.go.jp/english/int-activities/overseas-office/dc/0002.html

When you want to consult with Washington D.C. Office

https://www.pmda.go.jp/english/int-activities/overseas-office/dc/0002.html

3. How we provide a general consultation

To request for o
General Consult
At the time of su
the consultatio

Application Form for General Consultation

Please fill in the following fields with blue shading (* Required):

		Control No.	Click or tap here to
(1)	Application date*	Click or tap here to enter the text.	
	Phone number*	Click or tap here to enter the text.	

- Fill in the “Application form for General Consultation” on the PMDA website

- Apply to Washington D.C. Office via e-mail
  E-mail:
  Consultation[at]dc-office.pmda.go.jp
  (Note) To block unsolicited emails being sent to us, we request you to replace **[at]** with **@**

- No Japanese consultation materials required

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For your further understanding（PMDA)

https://www.pmda.go.jp/english/int-activities/industry/0001.html