PMDA's Experiences with New Drug Applications including Data from Multi Regional (Asian) Clinical Trials

Yasuto Otsubo
Reviewer, Office of New Drug V Pharmaceuticals and Medical Devices Agency (PMDA)
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Today's topic

- Current situation on Multi Regional Clinical Trials (MRCTs) in Japanese NDAs
- Guidelines on Multi Regional Clinical Trials (MRCTs)
- Activities of Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC)
- Summary
Current Situation of MRCT in Japanese NDAs

Number of Approved Drugs

- Total
- MRCT
- Bridging Strategy
- % of MRCT

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Approved new drugs based on MRCTs in Japan (FY2006-2013)

FY2006  Tolterodine, Losartan, Trastuzumab, Insulin-Glulisine, Tadalafil, Peramivir, Everolimus
FY2009  Panitumumab, Travoprost/Timolol, Temsirolimus, Laninamivir, Nilotinib, Dabigatran, Trastuzumab
FY2010  Promipexole, Edoxaban, Dasatinib, Indacaterol, Linagliptin, Gefitinib, Everolimus, Denosumab, Aripiprazole, Olanzapine, Exenatide, Crizotinib
FY2012  Bevacizumab, Pertuzumab, Lixisenatide, Ranibizumab, Regorafenib, Indacaterol/Glycopyrronium, Paliperidone, Vilanterol/Fluticazone, Bevacizumab, Aflibercept, Riociguat, Tadalafil, Afatinib, Turoctocog alfa, Ranibizumab, Pazopanib, Goserelin, Everolimus, Tolvaptan, Favipiravir, Tapentadol, Tofogliflozin

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Red: Asian Clinical Trial
### Approved new drugs based on MRCTs in Japan (FY2014-2016)

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs</th>
</tr>
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Motivation for Asian Clinical Trial implementation

相似性在民族因素（内在因素）
- 纤维素和频率的代谢酶 polymorphisms
- 基因型

使用来自亚洲临床试验的数据用于 NDA 在其他亚洲地区以及日本
- 满足在每个地区 NDA 的要求

增加临床试验的可行性
- 足够的样本大小以实现研究目标
- 美国/欧盟的临床开发滞后
Countries/Regions Selected for Asian Clinical Trial with Japan (2010~2016)

Number of studies (Pivotal study only)

South East Asia

- South Korea: 5
- Hong Kong: 3
- Malaysia: 7
- Indonesia: 8
- Taiwan: 22
- China: 27
- India: 5
- Singapore: 3
- Philippines: 3
- Thailand: 2

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Proportion of Japanese subjects in each Asian Clinical Trial

- **0~25%**
  - e.g. Gefitinib, Levetiracetam

- **25~50%**

- **50~75%**

- **75~100%**
  - e.g. Edoxaban, Levodopa/Carbidopa
## Guidelines on MRCTs in Japan

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Issued year</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic principles on Global Clinical Trials</td>
<td>2007</td>
<td>➢ Basic requirements to conduct a MRCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Basic points to consider in designing a MRCT</td>
</tr>
<tr>
<td>Basic principles on Global Clinical Trials (Reference Cases)</td>
<td>2012</td>
<td>➢ Points to consider for MRCTs in East Asia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ General points to consider for MRCTs</td>
</tr>
<tr>
<td>Basic principles for Conducting Phase1 Trials in the Japanese Population Prior to Global Clinical Trials</td>
<td>2014</td>
<td>➢ Reference cases regarding the necessity of conducting a phase1 trial in the Japanese population</td>
</tr>
</tbody>
</table>

ICH E17 Guideline: MRCT

The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.
What will be changed after implementation of the E17 guideline?

2.2.5 Estimation of an Overall Sample Size and Allocation to Regions

Allocation to Regions

For purposes of sample size planning and evaluation of consistency of treatment effects across regions, some regions may be pooled, if subjects in those regions are thought to be similar with respect to intrinsic and/or extrinsic factors, which are relevant to the disease area and/or drug under study.

If some information about regional differences in patient demographics and the impact of intrinsic and/or extrinsic factors on the treatment effect was obtained from exploratory MRCT, some regions might have been pooled into one “Pooled regions”.
2.2.5 Estimation of an Overall Sample Size and Allocation to Regions

Allocation to Regions

- It should be discussed at the planning stage how the analyses of pooled regions and/or pooled subpopulations may provide a basis for the regulatory decision-making for relevant regulatory authorities. This should also be specified and be described in the study protocol in advance.

- It is recommended to have early discussions with the different regulatory authorities involved in the MRCT and to obtain regulatory input on analysis strategy such as “pooled region”.

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What will be changed after implementation of the E17 guideline?

2.2.7 Statistical Analysis Planning to Address Specific Features of MRCTs
Examination of Regional Consistency

The statistical analysis plan should include a strategy for evaluating consistency of treatment effects across regions, and for evaluating how any observed differences across regions may be explained by intrinsic and/or extrinsic factors.

▶ The way to evaluate consistency of treatment effects across regions (e.g., primary endpoint, secondary endpoints) should be described in the statistical analysis plan.
Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs

- Plan, design, and coordinate training for Asian regulatory authority staff.
- Provide training opportunities including on-site training.
- Help raise the level of regulations in Asia as a whole.

(1) Training seminar by PMDA, local prefectures and industry

(2) Assign to local site

(3) APEC Training Centre for Clinical Trial and Pharmacovigilance
What we do at PMDA-ATC

- Organize training programs held at PMDA and overseas.
- Exchange staff members for on-the-job training.
- **Training themes**
  - Best regulatory practices in product review, safety info analysis, etc.
  - ICH, IMDRF, IGDRP, ICCR, PIC/S guidelines.
  - Specific topics per request by partner countries.
<table>
<thead>
<tr>
<th>Theme</th>
<th>Date</th>
<th>Place</th>
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<tbody>
<tr>
<td>Pharmaceuticals Review</td>
<td>25-29 July</td>
<td>Tokyo (PMDA)</td>
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<tr>
<td>Pharmaceuticals Review</td>
<td>26-29 Sept</td>
<td>Bangkok, Thailand</td>
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<tr>
<td>Medical Devices</td>
<td>7-11 Nov</td>
<td>Tokyo (PMDA)</td>
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<td>Good Review Management#</td>
<td>15-17 Nov</td>
<td>Chinese Taipei</td>
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<td>Good Manufacturing Practice (GMP) Inspection*</td>
<td>5-9 Dec</td>
<td>Toyama, Japan</td>
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<td>Multi-Regional Clinical Trial (MRCT)#</td>
<td>23-26 Jan</td>
<td>Tokyo (PMDA)</td>
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<tr>
<td>Pharmacovigilance#</td>
<td>6-9 Feb</td>
<td>Tokyo (PMDA)</td>
</tr>
</tbody>
</table>


- *supported by PIC/S
- # conducted as APEC-LSIF-RHSC CoE Pilot Workshop

- Ad-hoc trainings conducted per request from regulatory authorities
PMDA-ATC MRCT Seminar 2017 in PMDA (23-26 Jan)

- Total of 32 regulators from 14 economies* joined.

  *Brazil, China, Chinese Taipei, Indonesia, Malaysia, Mexico, Myanmar, Nepal, Papua New Guinea, Peru, Philippines, Sri Lanka, Tanzania and Thailand

- Lectures and case studies by staff members from PMDA, as well as those from an overseas regulatory agency, the JPMA and the academia.

<Lectures> <Case studies>

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https://www.pmda.go.jp/english/symposia/0102.html
Our plans for the future

- Continue holding PMDA-ATC seminars at PMDA.
- Increase the number of PMDA-ATC seminars held Japan/overseas to provide more chances to “train the trainer”.
- Plan PMDA-ATC Seminars with more flexibility.
  - theme, duration, mock review etc.
- Conduct hearings to find out the training needs.
- Work collaboratively with training providers for regulatory convergence.
PMDA – future direction in Asia

- Disseminate PMDA’s accumulated knowledge and experiences to promote regulatory science.
- Provision of hints for betterment of the regulations in participants' regulatory authority.
- More contribution to public health as a result of improvement in regulations.

PMDA promotes capacity building activities in Asia
Key message

PMDA accumulates knowledge and experiences of MRCTs

Facilitate the implementation of MRCTs including South East Asia

Establishment of the guidelines on MRCTs

New drug development ↑
Early access to innovative new drug ↑
In South East Asia
Ask