A Review of the CDx Process in Japan and China

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Diaclaimer

The following presentation reflects my own personal views and not that of my employer, Dako North America, An Agilent Technologies Company

Agenda

Japan CDx regulatory considerations

- CDx Guidance in Japan
- Experience with PMDA

China CDx regulatory considerations

- IVD Regulations in China
- Experiences and Challenges in CDx Registration

IVD CDx (Companion Diagnostic)

Companion Diagnostic (FDA guidance)

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. (device include reagent, instrumentation, software)

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product.

Drug approval will depend on the Device approval and vice versa

Oncology Market in Asia

The Oncology Market is growing rapidly in Asia, due to aging population and health care changes, including access to medicines

Companion Dx growth expected as a result

Companion Diagnostics Market to Hit $5.6 Billion in 2019*

Fastest growth in China: Estimates of market value expanding at a Compound Annual Growth Rate (CAGR) of 17.3 percent to reach $33.3 million by 2020**

- Breast and Lung Cancer among top indications

The regulatory landscape for CDx in Asia is complex

IVD regulations are evolving and careful planning is required

*FierceDiagnostics, July 2015
**Drug Discovery and Development, July 2015

Japan CDx regulatory considerations

- Prior to placing IVD on the Japanese market, a foreign manufacture:
  - Must appoint MAH located in Japan
  - Must be accredited by MHLW (Ministry of Health Labor and Welfare)
  - Must apply for IVD approval

- CDx
  - Likely considered as class III IVD (high risk product)
  - Approval by MHLW
  - Provide product QMS file and product technical file prepared according to Guide to the Japanese Revised Pharmaceutical Affairs Law
  - Compare to a Japan predicate if available

Japan CDx regulatory considerations

Japan has specific regulatory guidance on CDx product:

Technical Guidance on Companion Diagnostic agents and Related Pharmaceutical Products

by PMDA (Pharmaceuticals and Medical Devices Agency)

Ihatsu no. 1224029

December 24, 2013

Provide the guidance on Clinical studies during development of pharmaceutical products related to companion diagnostic agents.

Points to notes include:

- Handling of biomarker-negative
- The need for prospective confirmatory clinical studies
- Evaluation of Clinical significance of companion diagnostic agents
- Studies to evaluate the concordance of companion diagnostic agents

Japan CDx regulatory considerations

Japan has specific regulatory guidance on CDx product:

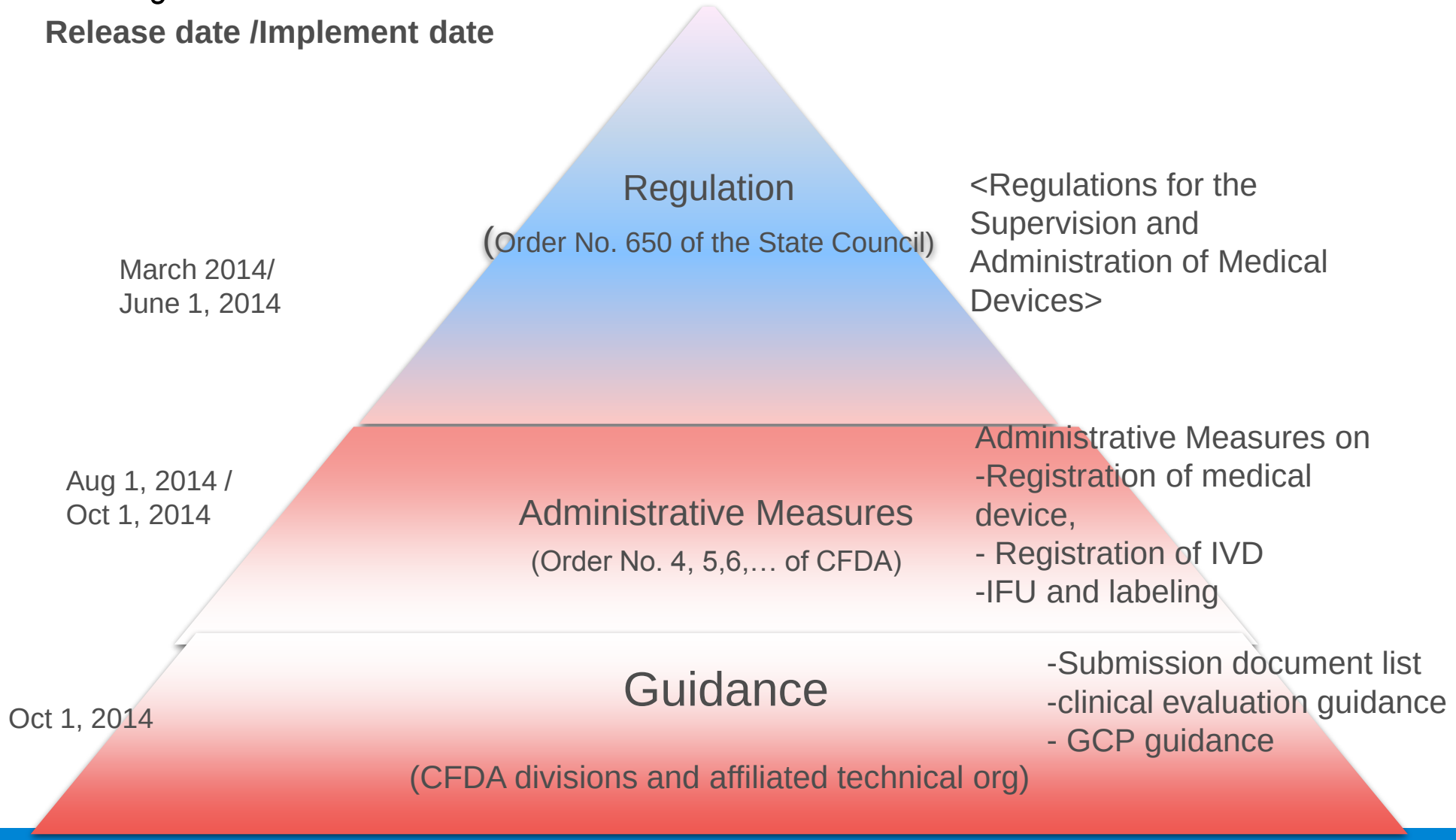
Experiences:

- PMDA is interested in US FDA filing strategy (Rx and CDx)
- Expect co-submission and co-approval of Rx and CDx (CDx submission maybe within one month of Rx submission)
- Representation of Japanese patients
- Central testing can be done outside of Japan
- Consultation highly recommended, especially clinical consultation
  - cut off determination, bridging study protocol review, etc.
  - Pre-consultation (free)
  - Consultation (fee required)
  - 4 way meeting (PMDA Rx/Dx/pharma/Dx developer)
  - Can request meeting with MHLW
- Prepare to provide data (i.e. case report form) from central testing lab(s) to support clinical data audit
- Apply for reimbursement approval

China CDx regulatory considerations

China Regulation Scheme as a review

Release date /Implement date



China CDx regulatory considerations

- Prior to placing IVD on the China market, a foreign manufacture:
  - Must appoint agent located in China
  - Possibly need quality inspection from CFDA

- CDx
  - Considered as Class III IVD (high risk product)
  - Approval by CFDA
  - Provide product QMS file and product technical file prepared according to regulations and guidance from CFDA

China CDx regulatory considerations

- No Technical guidance on CDx products by CFDA
- CFDA co-review between Medical Device and Drug review centers not formally established
- CMDE (Center for Medical Device Evaluation) indicated they may not follow approval process granted to products approved prior to 2014

- Basic requirements since 2014:
  - Provide kit for local validation testing (type testing - 3 lots) required prior to clinical study
  - Local assay clinical trial to demonstrate drug efficacy (novel product) or, Concordance testing to a predicate available (Me-too)
    - A minimal of 3 sites (w/ certification of clinical testing) (commercial labs not valid)
    - At least 1000 samples, ~300 positive

China CDx regulatory considerations
Regulatory Pathways

An option for new Medical Devices in China

CFDA Notice on the Release of Special Approval Procedure (Tentative) for

Innovative Medical Devices

SYJXH [2014] No. 13 Published on Feb. 7, 2014

- Single contact person to manage review
- Classification category is decided in parallel with technical review
- Advanced feedback from Test Centre
- Special review team pointed
- Priority processing

China CDx regulatory considerations
Regulatory Pathways

CFDA Notice on the Release of
Special Approval Procedure (Tentative) for **Innovative Medical Devices** (2014, Feb)

Specific Requirements:

- Patent Qualification

  Owns the patent of the core technology of the product, or owns the patent or right to use in China; or the application for the patent has been published

- Product Value

  Main operating principle/working mechanism is original, demonstrates fundamental improvement in terms of performance, the technology is globally advanced and shows obvious value in clinical application.

- Research Progress

  Completed the early stages of R&D, process is authentic and controlled with complete and traceable research data.

Procedures:

- Apply prior to product registration
- CFDA review and determination to grant pathway is made in 40 working days

China CDx regulatory considerations
Regulatory Pathways

CFDA Medical Device **Priority Evaluation Program:**

- Came into force in January 2017
- Class III devices manufactured in China and Class II and III devices from foreign manufacturers.
- May qualify for CFDA priority evaluation
  - Device Meeting one of the criteria:
    - Devices that diagnose or treat rare disorders and provide significant clinical advantage
    - Devices to diagnose or treat malignant tumors and provide significant clinical advantage
    - Devices to diagnose or treat diseases affecting elderly populations and that do not currently have effective diagnosis or treatment options
    - Devices to treat children and that provide significant clinical advantage
    - Devices that currently have no predicate products in China and that are urgently needed for public health purposes
  - Devices that fall under the National Science and Technology Major Project or the National Key Technologies R&D Program
  - Other devices for which high-priority evaluation is deemed necessary
- Application to the pathway made at the time of registration

China CDx regulatory considerations

Experiences and Challenges in Companion Diagnostic:

- Although IVD clinical testing must occur at government certified hospitals, drug trials can proceed in commercial labs
  - Creates a dilemma on CDx clinical trial design (Rx and CDx)

- CDx clinical data
  - CMDE is open to review therapeutic clinical study data to support the CDx clinical claim in support of CDx product registration in China. (the therapeutic clinical study could be global multi-center trial with appropriate Chinese patient representation).
  - the 1000 banked samples comparison study with predicate device is still required.

- Interaction with CFDA/CMDE
  - No formal consultation pathways, Informal discussions are common
  - No formal co-review/approval processed
  - Less flexibility and unclear path to discuss creative approaches, while still meeting regulations.

- Drug/Dx and KOL's will need to drive the discussions with CFDA, to underscore the importance of co-submission and co-approval process to enable timely availability of new cancer treatments to patients in China

Summary:

- Japan has a CDx pathway
  - CDx co-development guidance
  - Co-review/approval process
  - PMDA consultations

- China does not have CDx pathway formally
  - Moving to consider how clinical utility can be added for CDx claim
  - Co-review/approval not formally established

Thank you and Question?