Drug Development in Japan – A Clinical View

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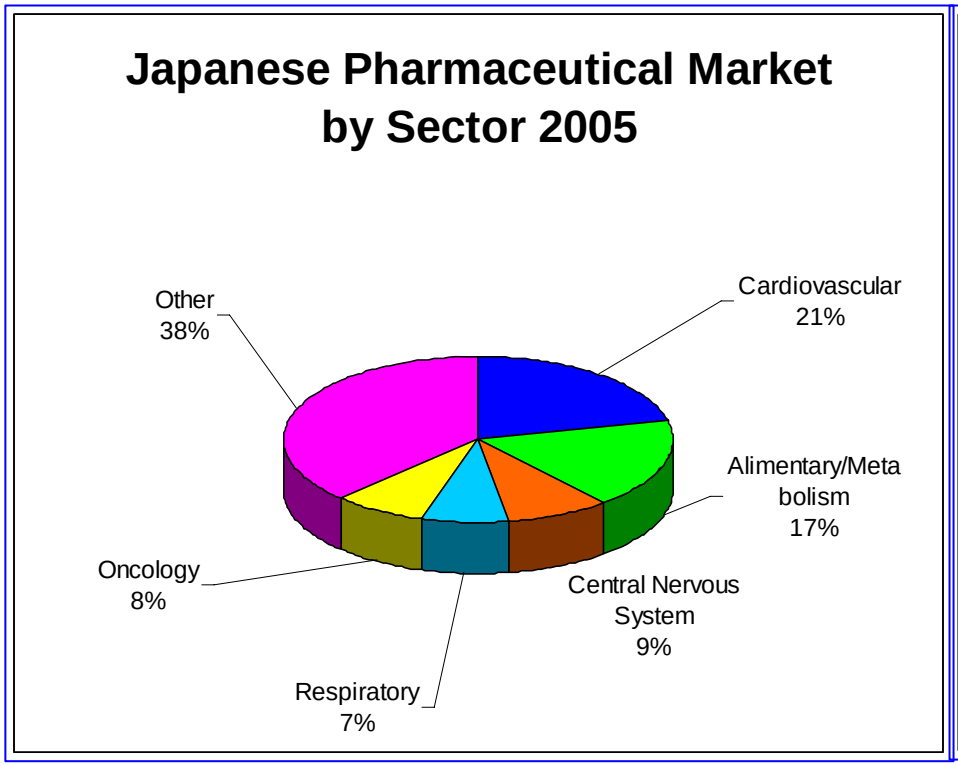
- Employee of Celgene Corporation
- Views presented in these slides represent my own views and do not necessarily represent the views of Celgene Corporation or Celgene KK

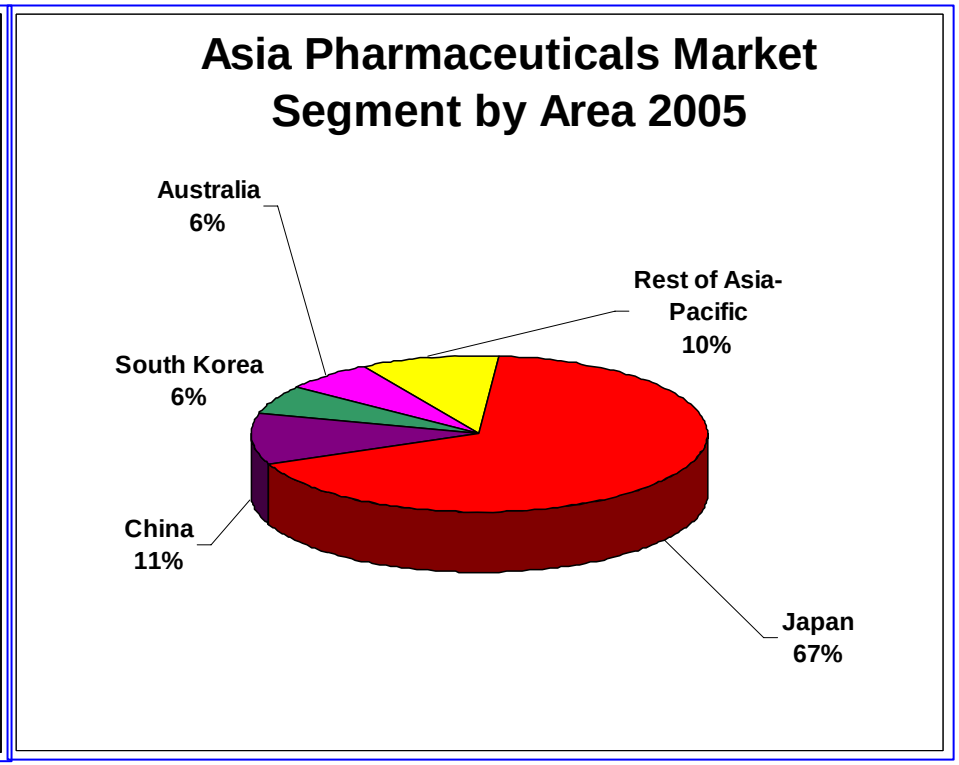
Outline of this talk

- General concepts in Japanese drug development
- Important recent developments
- Japanese regulatory agency:
  - Who are they
  - How they think
  - What they are looking for
- Special considerations for biologicals and combinations

Japan Overall Pharma Market

- Total market value in 2005 was $65.5 Billion USD.
- By 2010 the Japanese pharmaceuticals market is projected to reach $70.8 Billion in value
- 2nd largest individual market in the world after U.S.
- The Japanese market generates 67% of the Asia-Pacific market





Source: JETRO

Issues to consider

- Regulatory barriers
  - ICH does not cover all of Japan drug development
  - GCP in Japan is not GCP
- Language barriers
- Clinical practice differences
- Clinical investigators
- Operational differences and barriers
  - Many originate from J-GCP
- What works in the US/EU won’t work in Japan

Terminology

- PMDA →
  - Pharmaceutical and Medical Devices Agency
  - Japanese counterpart to the FDA
  - operational aspects of drug development
- MHLW →
  - Ministry of Health, Labour and Welfare
  - Japanese counterpart to the Dept of HHS
    - Higher degree of involvement in drug development
  - Ensures that public's interest is taken into account
  - Ultimately responsible for drug approval

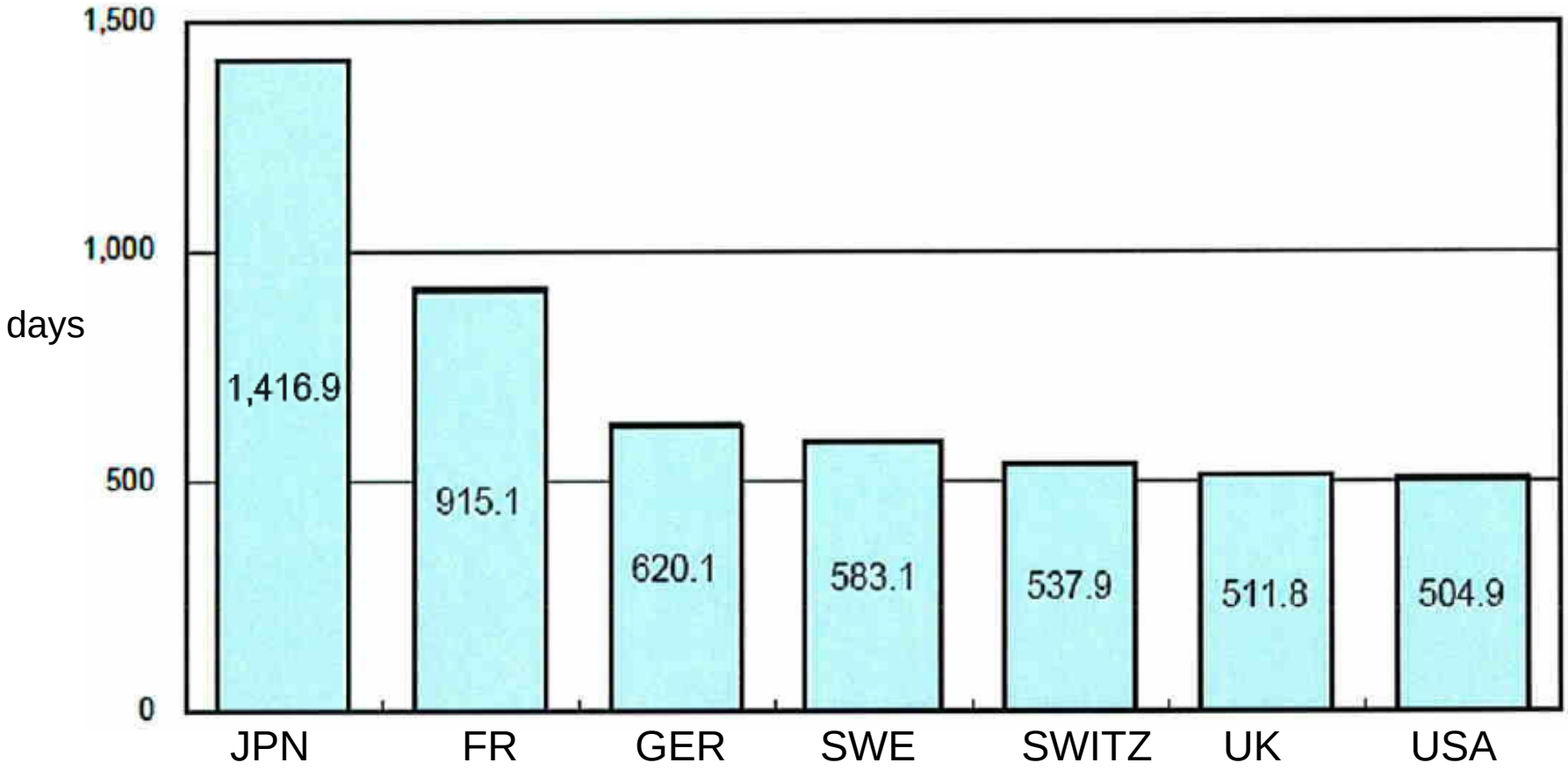
PMDA Functions

- Organization: ~300 people; few with M.D. background
- Review of drug application submissions
- Review of safety reports
- Payment of damages to Japanese patients who have incurred health damages from approved drugs
  - “Infection relief fund” contributed by manufacturers: Compensation paid to victims of severe infections associated with products
- Safety
- “Drug-lag”

Brief history of drug safety issues in Japan

- Thalidomide and teratogenicity
- Sorivudine and interaction with 5-FU
- HIV-contaminated plasma derived products (factor VIII)
- HCV-contaminated plasma derived products (fibrinogen; factor IX)

Drug-lag



Average time (days) from first approval anywhere in the world to approval in each country (days) for top 100 drugs in 2004

Source: 出典：日本製薬工業協会 医薬品産業政策研究所 リサーチペーパーNo.31（2006年5月） IMS Lifecycle より引用

PMDA

- To identify possible regulatory issues and provide possible solutions
- Very high concern for safety
- Safety confirmation studies and post-marketing data are increasing in oncology

PMDA/ MHLW

- For most drug developers, the primary contact will be with the PMDA
- Equally important, less frequent interactions with the MHLW

- Both are
  - Highly accessible
  - Welcome informal meetings/questions
  - Willing to engage in dialog

Path to approval

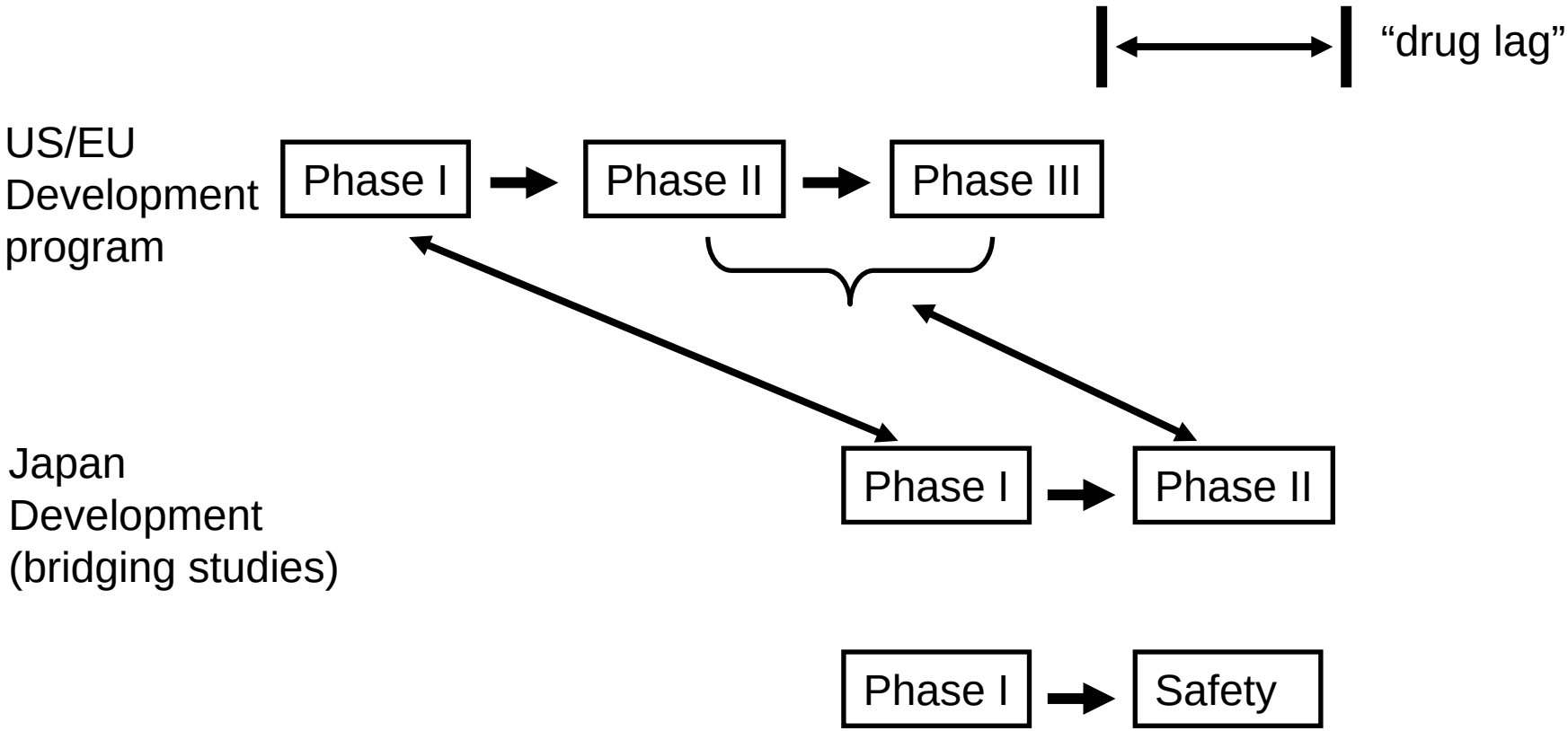
- Standard strategy
  - Phase I → Phase II → Phase III
  - Non-traditional approaches

- Bridging strategy
  - Evidence or rationale that drug efficacy and safety in non-Japanese patients can be extrapolated to Japanese patients
  - Typically, a “bridging study” is phase I/II study that mirrors the experimental arm of the study that the “bridging study” bridges to

Stand-alone strategy

- Standard phase I, II then III
- Small scale single arm Japanese clinical trials
  - Strong scientific rationale in orphan indication and no standard therapy, with strong interest from the Japanese medical community.
  - Example: 28 patient “clinical experience” was sufficient for an mAb → led to approval in Japan ahead of the ROW
  - Example: Enrollment of Japanese patients in clinical studies conducted outside of Japan → led to approval in Japan without a Japanese clinical trial
- No Japanese clinical trials:
  - “Petition” strategy: Situations of high medical need. The agency in very rare situations have accepted foreign data only

Bridging strategy



“Private importation”

- “Drug-lag” creates need/demand for un approved drug
- Physician can directly “import” and buy an unapproved drug on behalf of patient
  - Physician takes responsibility
  - Importer companies can facilitate
- Different from NPP and compassionate use programs
- Potential issues
  - Example: AEs occurring in private import uses may not be reported to the drug company, and information on unexpected AEs in Japanese patients may not be disseminated to physicians and investigators

Recent important developments

- Prioritization of consultation meetings
- MHLW Committee on Unapproved Drugs

Consultation meetings

- Informal meetings (“jizen mendan”):
- Formal meetings (“chiken soudan”):
  - Prioritization based on a point system has greatly relieved delays in scheduling meetings
- Japanese documents are preferable
  - Tables/Figures in English
  - High quality translation is critical
  - High quality interpreter is critical

MHLW Committee on Unapproved Drugs

- Committee of academic physicians and investigators appointed by the MHLW
  - Committee monitors every new drug approved in four key countries and meets every 3 months:
    - US, Germany, France, UK
  - A public meeting
  - Gives a priority “score”
    - The MHLW may contact the sponsor or agency with outcome of evaluation
  - Not a binding recommendation

Special Consideration for Biologicals

- PMDA Organizational structure
  - No CBER equivalent
  - PMDA “Office of Biologics”
    - As of July 2007: 24 staff members (out of total ~300 at PMDA)
      - 1 director, 2 review directors, 2 deputy review directors, 19 reviewers
    - Divided into teams
      - Vaccines, blood products, cells and tissue engineering products, gene therapy, biotechnological products (recombinant proteins)
- Special concerns
  - Biologicals have a higher risk of safety concerns (infectious)
  - Source of albumin (prions)
    - First to approve recombinant albumin
  - Source of blood derived products (Hep B/C, HIV)

Special Considerations for Biologicals

- "Biological products"
  - (containing human plasma derivatives)
  - Vaccines, Animal extracts, CHO cell derived recombinant proteins
  - "subject to particular attention from public health point of view, PAL Article 2.5)
  - Record retention (10 yr; 30 yr if product contains human plasma derivatives), periodic surveillance reports to MHLW, additional labeling for "biological products"
- "Specified biological products"
  - Blood/plasma derived products, human cell/tissue based, Human extracts
  - "biological products with particular care to prevent onset and transmission of infection (PAL Article 2.6)
  - Added requirements: informed consent, record retention (30 yr), "risk and benefit" on package labeling
- "Biological products – Exempt"
  - Recombinant proteins manufactured from non-pathogenic sources
  - Example: E coli-derived insulin

Increasing numbers of consultation meetings for biologics and cell therapeutics

	2004	2005	2006
Biologics	8	12	11
Blood products		3	7
Cell therapy		0	5
Total	8	15	23

Source: Presentation given by Katsutoshi Tanaka, Review Director, PMDA, at the Drug Evaluation Forum 2007

Development of drug combinations

- Generally pragmatic approach
  - Is the combination clinically important?
    - Reliance on the opinion of key physicians and investigators for scientific rationale and importance of combination
- Consider whether one or both drugs are “investigational” drugs in Japan
  - What is considered “standard use” in US/EU may be an unapproved usage in Japan

Example

- Drug A is approved when used in combination with drug B for a given indication X in US and EU
- Drug B is recognized in US / EU as a standard agent for the indication X
- In Japan: if drug B is not approved for this indication, special regulatory considerations are needed, even if drug B is approved and available in Japan for a different indication
  - Agency does not wish to promote unapproved usage of drug B
  - Possible solutions:
    - Co-develop drug B as an investigational agent (with the eventual filing for approval)
    - Use of drug B through “private importation” mechanism

Summary / Conclusions

- Drug development in Japan need not be complicated or mysterious
  - Regulations are different, but regulators have flexibility
  - High degree of collaboration between agency/ministry, physicians, patients and industry is feasible
  - Agents with strong science or clinical need receive attention
- Because of differences between Japan versus US/EU, good understanding of the Japanese regulations can lead to commercialization advantages and opportunities
  - Drugs available elsewhere but not approved in Japan
- Key: Close communication with both the PMDA and the MHLW
  - For foreign pharmaceutical/biotech companies, a strong in-house Japanese regulatory affairs group or close working relationship with external consultants familiar with Japanese regulations is a must