第2回EMAの最新動向と国際協調の現状についての講演会
平成23年5月24日（火）

FDA-CDER-OSEでの研修を通じて学んだこと

石黒 智恵子
安全 第1部

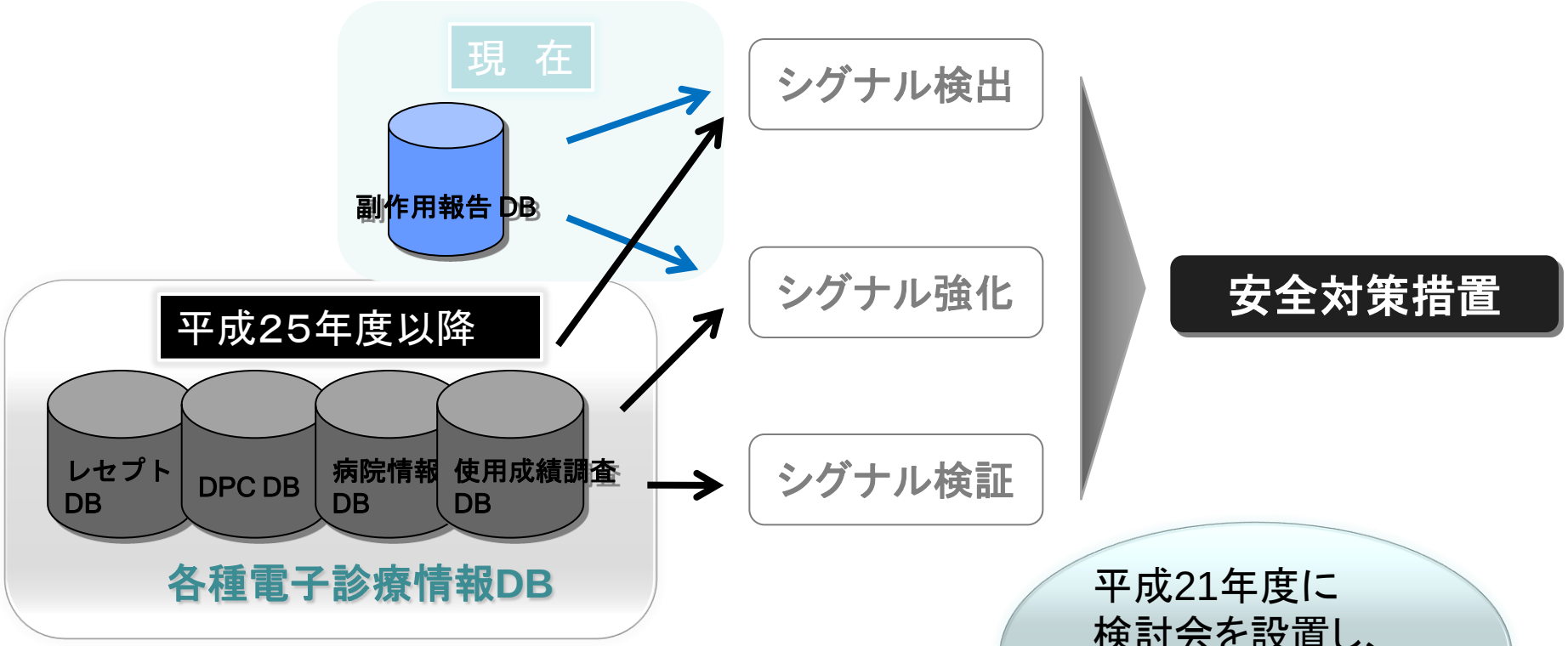
今日のおはなし

- 研修に行くことになった背景・動機
- FDA/CDER/OSEにおける研修内容
  - FDAにおける薬剤疫学を用いた安全対策業務体制

背景1

- PMDAの安全対策部門強化
  - 100名増員、Risk Manager設置、チーム細分化
- PMDA の薬剤疫学導入に向けて始動
  - **MIHARI project**
  - Medical Information for Risk Assessment Initiative
    - レセプト・電子カルテ等の電子診療情報データベースの2次利用による薬剤疫学研究評価体制の構築

【概念図】医薬品の安全性評価プロセスへの新たなDBの導入検討



平成21年度に
検討会を設置し、
各種電子診療情報
について検討開始

PMDA

電子診療情報等の安全対策への活用に関する検討会

協力 ⇧ 医療機関

委員として参加 ⇧ 大学等

検討内容（例）
- データの確保
- 各種DBの特性・限界
- 安全性解析方法
- 各種DBの活用方法

MIHARI Project

MIHARI

Medical Information for Risk Assessment Initiative

MIHARI ロードマップ

平成 21 年度
- MIHARI 立ち上げ
- 検討会設置
- 情報収集
- 方針策定
- 計画作成
- 基本試行調査

平成 22 年度
- 試行調査拡大
- データソース拡大
- 報告書作成
- 学会発表
- 計画見直し

平成 23 年度
- 試行調査拡大
- データソース拡大
- 中間取りまとめ
- 業務への適応 検討
- 報告書作成
- 学会発表
- 計画見直し

平成 24 年度
- 業務適応向け 試行調査
- 試行調査拡大
- データソース拡大
- 報告書作成
- 学会発表
- 計画見直し

平成 25 年度
- 業務適応向け 試行調査
- 試行調査拡大
- データソース拡大
- 最終取りまとめ
- 報告書作成
- 学会発表
- 次期計画作成

http://www.info.pmda.go.jp/kyoten_iyaku/mihari.html

背景2

- FDAにおける安全対策の強化
  - Vioxx事件を機に…
    - GAO (会計検査院）報告書
    - IOM（Insitite of medicine) 報告書
    - FDA Amendment Act (FDAAA)　Title IX　2007.9
      - FDAは添付文書などの変更を要求できる
      - 市販後のリスク検証・分析のための研究・試験を実施させることができる
      - 市販後のREMSの作成・実施を要求できる
      - FDAが自ら新しい電子的なデータ収集の仕組みを作る
        - » *sentinel initiativeの発足*

FDA訪問の目的

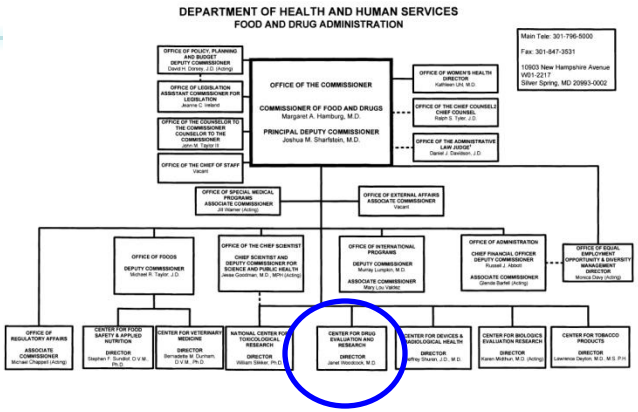
- Objective
  - FDAにおける疫学リソースを把握し、それらが審査・安全対策上どのように行政判断に活用されているのかを学ぶこと

→PMDAにおける薬剤疫学利用方針・体制整備に役立てる

研修先

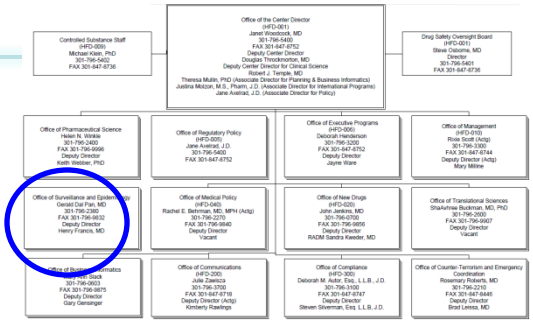
- Term: September 7 –December 3, 2010
- Location: FDA white oak campus
- Office: **FDA/CDER/OSE**
- Supervisor: Dr. Gerald Dal Pan

FDA Organization



- Office of the Commissioner
- ORA (Office of Regulatory Affairs)
- **CDER (Center for Drug for Evaluation and Research)**
- CDRH (Center for Device & Radiological Health)
- CBER (Center for Biologics Evaluation and Research)
- CVM (Center for Veterinary Medicine)
- CFSAN (Center for Food Safety and Applied Nutrition)
- Center for Tobacco Products
- National Center for Toxicological Research

CDER Organization



- OPS (Office of Pharmaceutical Science) ---OGD, ONDQA etc.
- **OSE (Office of Surveillance and Epidemiology)**
- OBI (Office of Business Informatics)
- ORP Office of Regulatory Policy
- OMP Office of Medical Policy
- Office of Communications
- Office of Executive Programs
- OND (Office of New Drugs) --- 6 offices, 18 divisions
- Office of Compliance
- Office of Management
- OTS (Office of Translational Sciences) ---OB(8D) & OCP (5D)
- Office of Counter-Terrorism and Emergency

研修が始まるまで

- 研修受入れ完了まで（約1年）
  - PMDA内の研修委員会で承認
  - PMDAからFDAへ研修の申し込み
    （FDAにおけるSupervisorとの面会　etc）

- 現地到着後
  - 面談
  - Goal, Objective, Strategyの設定

1. 基本情報
組織体制・役割

OSE Organization & Role

Immediate Office
Gerald Dal Pan, Director
Henry "Skip" Francis, Deputy

DRISK
(Division of Risk Management)
Claudia Karwoski, Director

DEPI
(Division of Epidemiology)
Judy Staffa, Director

DMEPA
(Division of Medication Error Prevention & Analysis)
Carol Holquist, Director

DPV 1
(Division of Pharmacovigilance 1)
Mark Avigan, Director

DPV 2
(Division of Pharmacovigilance 2)
Bob Boucher, Director

Director
Dr. Gerald Dal Pan
Since 2003

<u>Core Areas</u>
Pharmacovigiliance
Pharmacoepidemiilogy
Risk management
Medication Error prevention

OSE Organization & Role 2

Immediate Office
Gerald Dal Pan, Director
Henry "Skip" Francis, Deputy

DRISK
(Division of Risk Management)
Claudia Karwoski, Director

DEPI
(Division of Epidemiology)
Judy Staffa, Director

DMEPA
(Division of Medication Error Prevention & Analysis)
Carol Holquist, Director

DPV 1
(Division of Pharmacovigilance 1)
Mark Avigan, Director

DPV 2
(Division of Pharmacovigilance 2)
Bob Boucher, Director

IO Staffs:

Outreach and Communication,
Regulatory Affairs and Policy,
Regulatory Research,
Project Management,
Information Systems,
Contracts,
Administrative

OSE Organization & Role 3

Immediate Office
Gerald Dal Pan, Director
Henry "Skip" Francis, Deputy

5 Review divisions

DRISK
(Division of Risk Management)
Claudia Karwoski, Director

REMS review etc

DEPI
(Division of Epidemiology)
Judy Staffa, Director

Epidemiological review etc

DMEPA
(Division of Medication Error Prevention & Analysis)
Carol Holquist, Director

Medication Error review (Package, proprietary name)

DPV 1
(Division of Pharmacovigilance 1)
Mark Avigan, Director

DPV 2
(Division of Pharmacovigilance 2)
Bob Boucher, Director

Adverse event report review (AERS, data mining, etc)

2. FDA安全対策の人員体制 (市販前･市販後)

FDAの安全対策業務における昨今の変化

- Vioxx事件後、GAO、IOM、FDAAAを経て…
  - OSEとONDの関係性↑↑
    - Memorandum of Agreement (MOA) Between the OND and OSE, June 16, 2008
  - 全部門間の関係性↑↑
  - Equal Voice 09/16/10
    - Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions →Multi discipline
  - Safety First Initiative

承認前の安全対策体制

- Primary reviewers

  Disciplines usually included on the core review team are:

  - Clinical (Medical) from OND
  - Clinical Microbiology (for anti-infective products) from OND
  - Pharmacology/Toxicology (P/T) from OND
  - Medication Error (for proprietary name) from OSE DMEPPA
  - Product Quality (formerly CMC) from OPS-ONDQA
  - Risk management (for REMS submissions) from OSE DRISK
  - Biometrics (Statistical) from OTS-OB
  - Clinical Pharmacology from OTS-OCP

Reviewers from OSE/DPV or DEPI, if needed.

市販後の安全対策体制

- **OSE staff**
  - AERSからのシグナル検出
  - シグナルを見つけたらONDにrecommendation
  - ONDなどの他部署からのconsultationを受けてレビュー

- **OND staff**

  企業から直接提出されたものをレビュー
  必要に応じてOSEへconsultation
  OSEからのrecommendationへのresponse

Tracked Safety Issue (TSI) in DARRTSで共有

OSE-OND間のMTG

- Data-mining meeting (depends..)
- Issue specific meetings (ad-hoc)
- OSE-OND safety meetings (regularly)
- Administrative rounds (regularly)
- FDAAA Section 915 NME and Non-NME meetings

  – その他、Safety issueに関する各種MTG
    - Advisory Committee for safety issue for safety issue
    - Regulatory briefing
    - Drug Safety Oversight Board (DSB)
    - Safety first meeting

3　FDAにおける薬剤疫学の実践

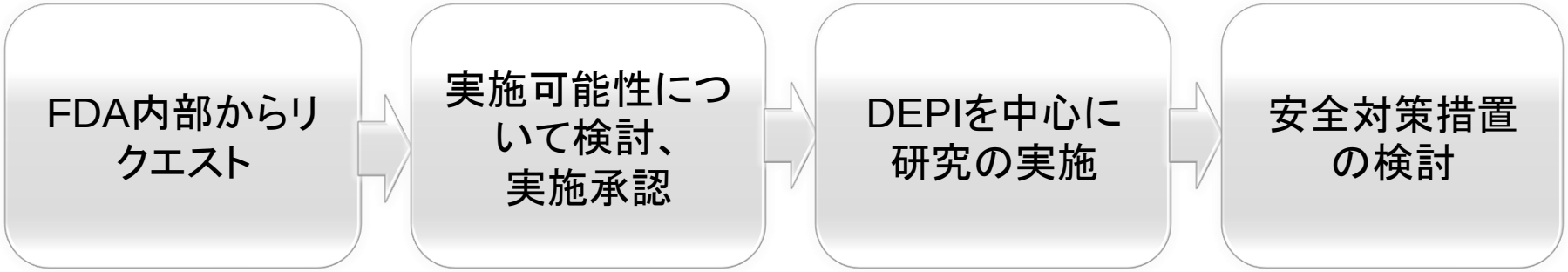
薬剤疫学に関連する部署

- 薬剤疫学研究の実施とレビュー
  - *OSE-IO (Regulatory Research Team)*
  - *OSE-DEPI (Epidemiologists)*
    - Extramural Collaborations
    - Intramural Research using GPRD

- *使用実態調査の実施*
  - *OSE-DEPI (Drug Utilization Team)*

薬剤疫学研究の実施

- OSE-IO (Regulatory Research Team)
- OSE-DEPI (Epidemiologists)
  - 企業横断的に実施する必要があるものについてはFDAが実施する



Example

- Rosiglitazone (Avandia®)

  AC meeting on Sep 15th 2010

  – Medicareを用いたCohort study

Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone

David J. Graham, MD, MPH
Rita Ouellet-Hellstrom, PhD
Thomas E. MaCurdy, PhD
Farzana Ali, BA
Christopher Sholley, BS
Christopher Worrall, BS
Jeffrey A. Kelman, MD, MMSc

Context Studies have suggested that the use of rosiglitazone may be associated with an increased risk of serious cardiovascular events compared with other treatments for type 2 diabetes.

Objective To determine if the risk of serious cardiovascular harm is increased by rosiglitazone compared with pioglitazone, the other thiazolidinedione marketed in the United States.

Design, Setting, and Patients Nationwide, observational, retrospective, inception cohort of 227 571 Medicare beneficiaries aged 65 years or older (mean age, 74.4 years) who initiated treatment with rosiglitazone or pioglitazone through a Medicare Part D prescription drug plan from July 2006-June 2009 and who underwent follow-up for up to 3 years after thiazolidinedione initiation.

Main Outcome Measures Individual end points of acute myocardial infarction (AMI), stroke, heart failure, and all-cause mortality (death), and composite end point of AMI,

ROSIGLITAZONE AND PIOGLITAZONE are the only thiazolidinediones currently marketed in the United States. In

使用実態調査の実施

- DEPI/Drug Utilization Team
  - 各種データベースを用いて解析を実施

Example

- Sibtramine (Meridia®)

  AC meeting on Sep 15th 2010
  - Meridia® prescription utilization in the outpatient retail setting
  - Meridia® prescription utilization by prescriber specialty in the outpatient retail setting
  - Meridia® patient counts by age and gender in the outpatient retail setting
  - Physician reports of patient BMI by age analysis
  - Concurrent Diagnosis Analysis
  - Sibutramine Duration of Use in a U.S.

ご清聴ありがとうございました