PMDA perspective: Ongoing activities and requirements for developing antibacterial agents for children

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PMDA Paediatric Drug Working Group

- One of the projects across multi-offices in PMDA
- Established in November 2011

International Collaborations

Collaboration at Pediatric Cluster

External Communications

Discuss pediatric issues with domestic stakeholders

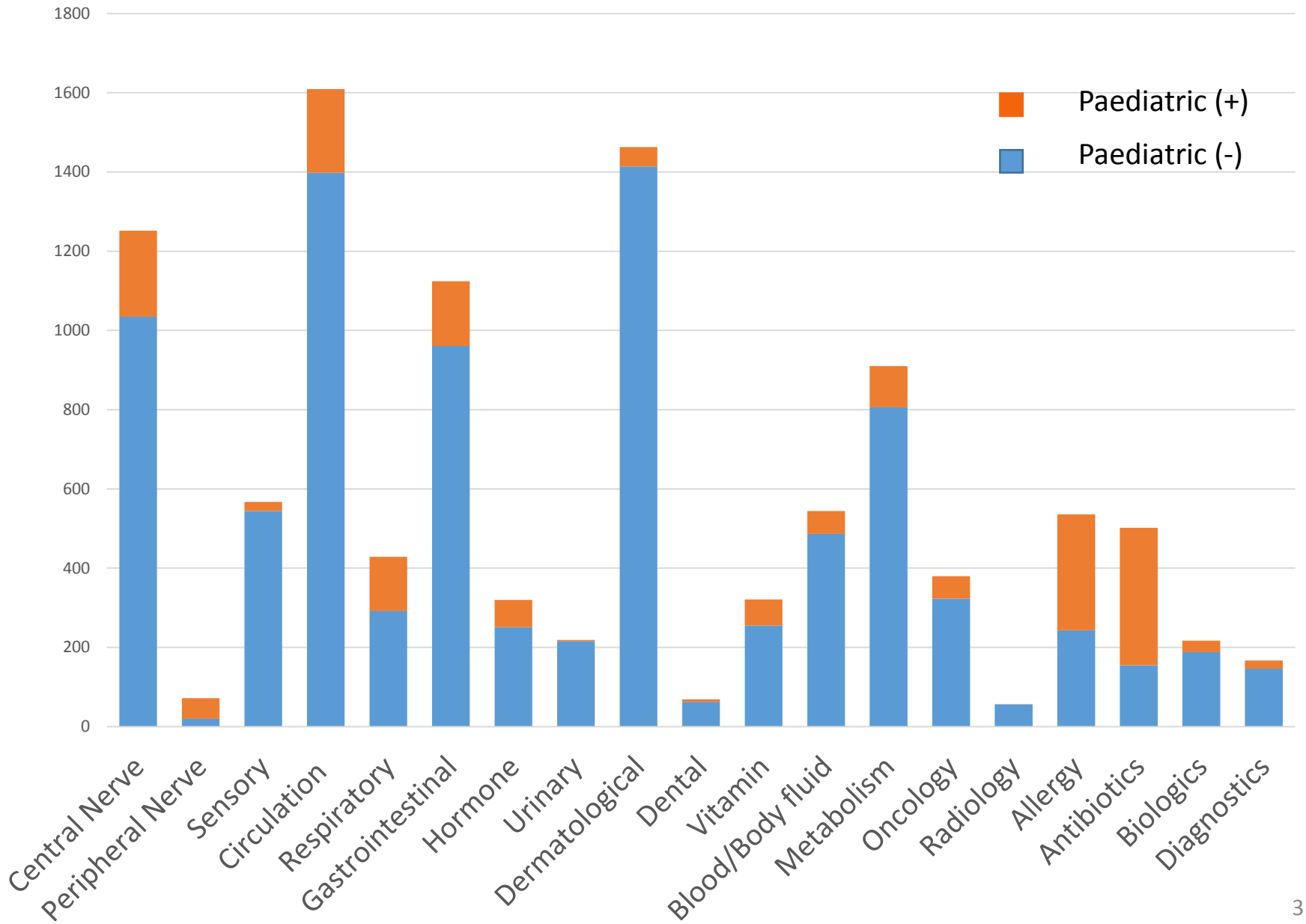
Members from Offices of New Drug, Office of Safety, Office of Regulatory Science, *etc.*

Analyses

Analyze and identify pediatric issues raised in past reviews and consultations

Internal Communications with Review Teams

Paediatric indication by therapeutic area in Japan



Useful tools for clinical development in Japan

- Development guidelines
  - Drafted by academic societies
  - Released by MHLW/PMDA
- Scientific advices by PMDA
  - Not mandatory
  - Most of products are received during development
  - From non-clinical to clinical development
    - Including R&D strategy

Guidelines for developing antibacterial agents for children in Japan

- ICH-E11 and E11 (R1)
  - Clinical Investigation of Medicinal Products in the Pediatric Population
    - 15 December, 2000
  - Q&A
    - 22 June, 2001
  - Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population
    - 27 December, 2017

- Guideline for Clinical Evaluation of Antimicrobial Agents (for adult & children)
  - PSEHB/PED Notification No. 1023-3, 23 Oct. 2017

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Guideline for Clinical Evaluation of Antimicrobial Agents

Attachment & Appendices

Guideline for Clinical Evaluation of Antimicrobial Agents

Attachment	Applicable Microorganisms
Appendix 1	Guidance for the Clinical Evaluation of Septicemia/Infective Endocarditis
Appendix 2	Guidance for the Clinical Evaluation of Skin and Soft Tissue Infection
Appendix 3	Guidance for the Clinical Evaluation of Infections in the Field of Orthopedics
Appendix 4	Guidance for the Clinical Evaluation of Respiratory Infection
Appendix 5	Guidance for the Clinical Evaluation of Infections in Urinary Tract and Genitourinary Field
Appendix 6	Guidance for the Clinical Evaluation of Sexually Transmitted Disease
Appendix 7	Guidance for the Clinical Evaluation of Intraperitoneal Infection
Appendix 8	Guidance for the Clinical Evaluation of Obstetrical and Gynecological Infection
Appendix 9	Guidance for the Clinical Evaluation of Infectious Colitis
Appendix 10	Guidance for the Clinical Evaluation of Ocular Infections
Appendix 11	Guidance for the Clinical Evaluation of Infections in the Otorhinolaryngological Field
Appendix 12	Guidance for the Clinical Evaluation of Infection in the Field of Dentistry/Oral Surgery
Appendix 13	Guidance for the Clinical Evaluation of Clostridium Difficile-Related Enterocolitis
Appendix 14	Guidance for the Clinical Evaluation of Pediatric Infection
Appendix 15	Guidance for Microbiological Evaluation

Guidance for the Clinical Evaluation of Pediatric Infection

Guideline for Clinical Evaluation of Antimicrobial Agents

Appendix 14

Guidance for the Clinical Evaluation of Pediatric Infection

1. Object

1.1. Major Target Strains

Basically, development of antimicrobial drugs in the field of pediatrics should be implemented after the safety and efficacy are confirmed in adults. Many microorganisms, therefore, may be isolated in clinical studies in adults.

For *Neisseria meningitidis, Bordetella pertussis*, and the like which are hardly isolated in clinical settings, the *in vitro* antimicrobial activities should be mainly used to list these strains as applicable microorganisms.

1.2. Target Diseases

- Acute tonsillitis, acute laryngopharyngitis, and scarlet fever

  If the indications for tonsillitis and infections caused by Streptococci are approved, the indication for "scarlet fever" can be additionally approved.

- Acute bronchitis and pneumonia

  Acute bronchitis in adults is not included in the indications of an antimicrobial drug, because this infection is mostly caused by virus. In most of the pediatric patients, however, it is caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, etc. If the efficacy against pneumonia in adults is confirmed, indications for pneumonia and acute bronchitis may be approved based on accumulated pediatric clinical cases of pneumonia and acute bronchitis

Guidance for the Clinical Evaluation of Pediatric Infection

Guideline for Clinical Evaluation of Antimicrobial Agents

1. Object
   - 1.1. Major Target Strains
   - 1.2. Target Diseases
2. Inclusion Criteria
3. Treatment Method and Duration
4. Evaluation Timing and Observation Items
   - 4.1. Evaluation Timing
     - 4.1.1. Baseline (day of the first dose, Day 0)
     - 4.1.2. Three Days after the First Dose (Day 3)
     - 4.1.3. End of Treatment (day of the end of treatment to 3 days after that)
     - 4.1.4. Test of Cure(7 to 10 days after the end of treatment)
   - 4.2. Observation Items
     - 4.2.1. Symptoms and Findings
     - 4.2.2. Collection of Specimens for Microbiology Test
5. Evaluation Method
   - 5.1. Clinical Effect
     - 5.1.1. Clinical Effect at the End of Treatment (End of Treatment)
     - 5.1.2. Efficacy Evaluation at the time of Test of Cure
   - 5.2. Microbiological Effect
   - 5.3. Easiness to take (only for oral drugs)

Ex) Target Diseases

- Acute tonsillitis, acute laryngopharyngitis, and scarlet fever
- Acute bronchitis and pneumonia
- Infections in Urinary Tract and Genitourinary Field (acute uncomplicated pyelonephritis, acute uncomplicated cystitis, complicated urinary tract infection, acute bacterial prostatitis, and acute epididymitis)
- Infections in the dermatology field (deep skin infection and infections secondary to injury, burn, and surgical wound)
- Infectious colitis (limited to bacterial enteritis caused by *Shigella*, *Salmonella*, *Campylobacter*, etc.)
- Septicemia
- Suppurative meningitis
- Pertussis

For the following infections, which should be listed in the indications in the field of pediatrics as well, clinical studies should be conducted in accordance with guidance in the other specialties.

- Infections in the otorhinolaryngological field (acute otitis media, and acute sinusitis)
- Infections in the field of orthopedics (suppurative osteomyelitis and suppurative arthritis)
- Intraperitoneal infections (peritonitis and Intraperitoneal abscess)
- Hepatobiliary infections (cholecystitis, cholangitis, and liver abscess)
- Infections in the ophthalmology field (blepharitis, hordeolum, dacryocystitis, orbital cellulitis [including eyelid abscess], keratitis, and endophthalmitis [including panophthalmitis])
- Infections in the field of dentistry/oral surgery (periodontal inflammation and maxillary ostitis)
- Skin and soft tissue infections (infections secondary to injury, burn, and surgical wound)
- Infections in the obstetrical and gynecological field (pelvic inflammatory disease, vulvitis, and bacterial vaginosis)

PMDA scientific advice: what we do

PMDA offers consultations to **give guidance and advice on clinical trials of drugs,** medical devices, and cellular and tissue-based products as well as on data for regulatory submissions.

In clinical trial advice for new drugs, PMDA **checks whether a proposed clinical trial complies with the requirements for regulatory submission**, taking into consideration the ethical and scientific aspects and reliability of the clinical trial as well as the safety of trial subjects, and also **gives advice to facilitate the improvement of the clinical trial**.

PMDA Profile of Services (2014-2015) http://www.pmda.go.jp/files/000151997.pdf

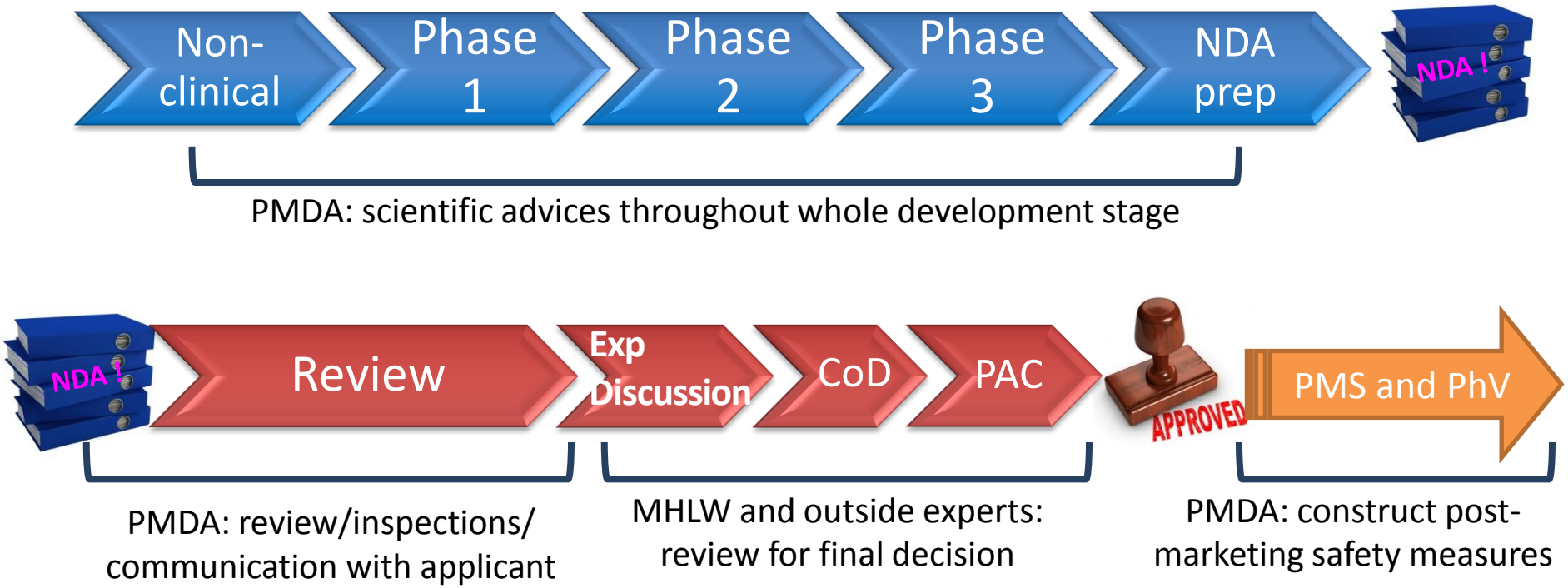
Scientific advice Category

So many categories to support a drug development - a sponsor can make advices basically on ANYTHING, ANYTIME!

NOTE: The list shown here is only on drugs. Another list available for medical devices

	Consultations		
Drugs	Procedural consultation for drugs		
	Consultation on bioequivalence testing, etc. for drugs	per co	
	Safety consultation for drugs	per cor	
	Quality consultation for drugs	per cons	
	Consultation before start of phase I study for drugs (non-orphan drugs)	per cons	
	Consultation before start of phase I study for drugs (orphan drugs)	per consu	
	Consultation before start of early phase II study for drugs (non-orphan drugs)	per consult	
	Consultation before start of early phase II study for drugs (orphan drugs)	per consulta	
	Consultation before start of late phase II study for drugs (non-orphan drugs)	per consultat	
	Consultation before start of late phase II study for drugs (orphan drugs)	per consultatio	
	Consultation after completion of phase II study for drugs (non-orphan drugs)	per consultation	
	Consultation after completion of phase II study for drugs (orphan drugs)	per consultation	
	Pre-application consultation for drugs (non-orphan drugs)	per consultation	
	Pre-application consultation for drugs (orphan drugs)	per consultation	
	Consultation on protocols of clinical trials for reevaluation and re-examination of drugs	per consultation	
	Consultation at completion of clinical trials for reevaluation and re-examination of drugs	per consultation	
	Additional consultation for drugs (non-orphan drugs)	per consultation	
	Additional consultation for drugs (orphan drugs)	per consultation	
	Consultation on GLP/GCP compliance for drugs (non-orphan drugs)	per consultation	
	Consultation on GLP/GCP compliance for drugs (orphan drugs)	per consultation	
	Prior assessment consultation for drugs (quality)	per consultation	
	Prior assessment consultation for drugs (non-clinical: toxicity)	per consultation	3
	Prior assessment consultation for drugs (non-clinical: pharmacology)	per consultation	2,
	Prior assessment consultation for drugs (non-clinical: pharmacokinetics)	per consultation	2,0
	Prior assessment consultation for drugs (phase I study)	per consultation	2,06
	Prior assessment consultation for drugs (phase II study)	per consultation	3,484
	Prior assessment consultation for drugs (phase II / III study)	per consultation	4,497,
	Consultation on drug product eligibility for priority review	per consultation	6,985,7
	Consultation on drug product eligibility for priority review (with pre-application consultation for drugs)	per consultation	823
	Consultation on pharmacogenomics/biomarkers (qualification)		
	Consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)		

Key milestones in product lifecycle



CoD = Committee on Drug PAC = Pharmaceutical Affairs Council

At the scientific advice

- Paediatric drug working group
  - Review needs of paediatric population
  - Ask plan for paediatric development, if the needs are recognized

Collaboration of scientific advice/review for paediatric medicine

Review Team

- Office Director
- Review Director
- Team Leader
- ADME
- CMC
- Pharmacology
- Biostatistics
- Toxicology
- Clinical
- Risk Manager

Paediatric W

- Group Leader
- CMC
- ADME
- Toxicology
- Pharmacology
- Risk Manager
- Pediatrician

Pharmaceutical affairs consultation on R&D strategy

- Scientific consultation service for academia and technology ventures (started 2011)
- 5 priority areas
  - Regenerative medicine (cell- and tissue- based products)
  - Cancer
  - Difficult-to-treat diseases and rare diseases
  - Pediatrics
  - Other than the above, products utilizing particularly innovative technologies

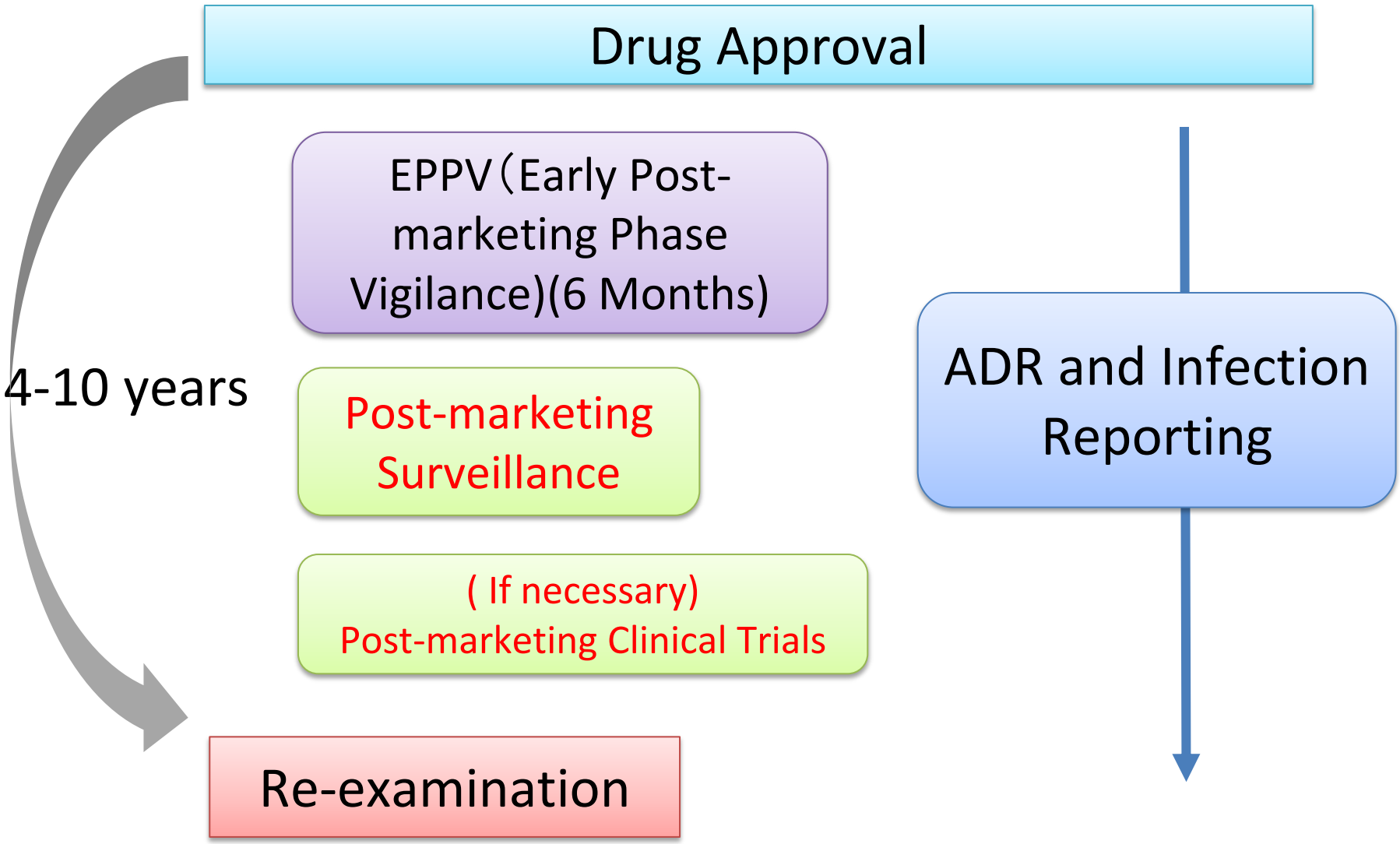
PMDA's challenge

- Advanced workflow of review / scientific advice
  - Receiving e-Submission of study data from Oct 2016
  - Modeling and Simulation project team
  - Sophisticated review/Consultation, Cross-Products Analysis
  - More effective and high quality Review, More efficient and Successful Development

- MID-NET Initiative
  - Utilization of real world clinical data

- Collaboration with Stakeholders
  - Japan
    - Academia, Industry
  - Global
    - Cluster with regulatory agencies, INC, DIA etc.

Framework of post-marketing safety measures in Japan



Post-marketing data collection

- Conducted in almost all drugs to collect efficacy and safety information under the real clinical use
- If necessary, investigation on long-term treatment, use in children, geriatrics and patients with renal or hepatic impairment, etc.
- Confirm concern Adverse Reactions (ARs), unknown ARs, and factors considered influential to efficacy and safety of the drug
- All-case surveillance are required when limited data available at the time of approval, orphan products

Advanced review/consultation with electronic data

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science
=Science of prediction and validation

Practical use of Innovative Medical Products

More rational & effective evaluation process for regulatory decision

NDA

e-Submission of study data

Use

Sophisticated review

- Each reviewer utilizes innovative assessment techniques

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

↓

Efficiency of the examination, sophisticated

Data Accumulation

Cross-Products Analysis

Use

- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Database

Use

Sophisticated Consultation

Use

- More evidence-based consultation

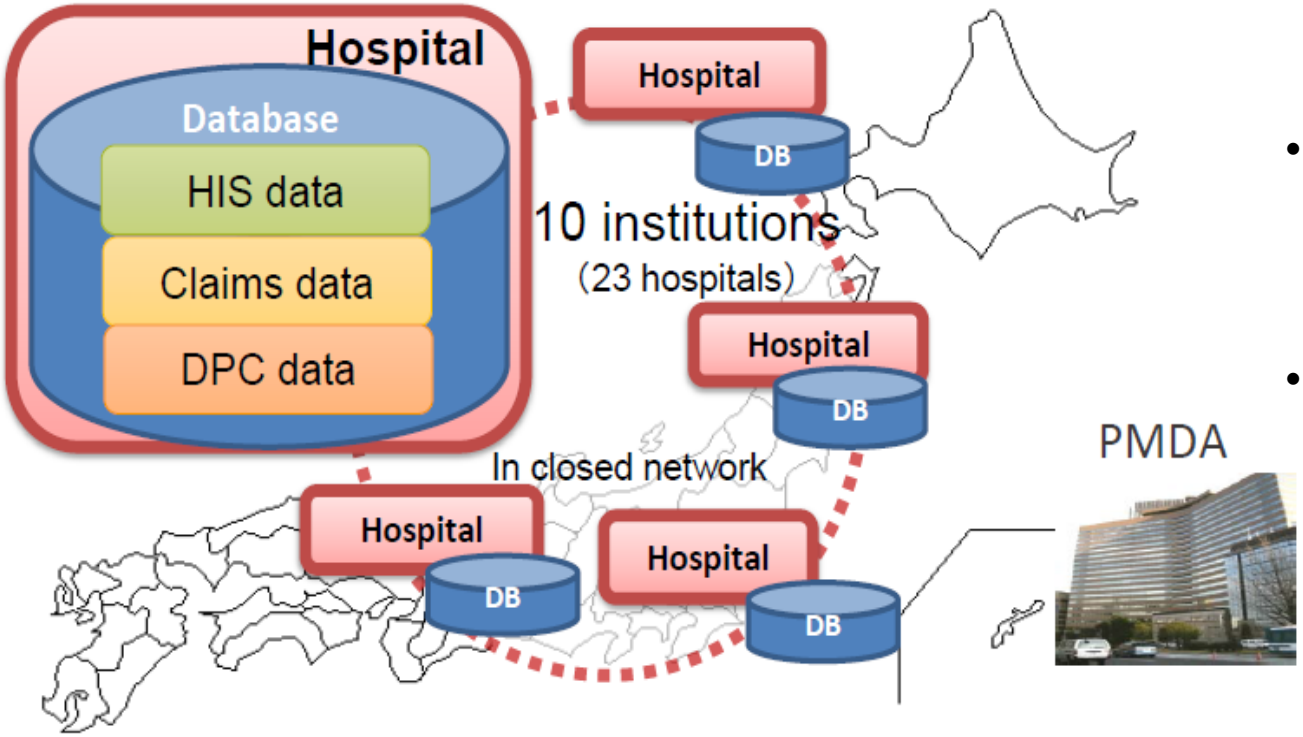
- Epoch-making proposal leading the world
- Proactive publication of guideline
- Rising success rate of development

↓

Efficiency of development (Shortening of the period, Cost reduction)

MID-NET Initiative

- MID-NET（ Medical Information Database NETwork） is initiated by MHLW / PMDA to establish the EMR DB network for post-marketing drug safety measures using electronic healthcare data



- Use of healthcare data from various data sources (incl. lab results)
- Data can be used almost real-time

Clinical Innovation Network (CIN)

(Improvement of Infrastructure for Clinical Study with Disease Registry)

【Background】
・Cost of developing a new drug or other medical products is rising over the world, especially in Japan compared to other countries.
・Recently, new approaches for clinical study with disease registry has been highly interesting.

【Brief overview of CIN】
・ The clinical study infrastructure in Japan is improved so that cost effective clinical studies are performed with disease registries, based on Regulatory Science. The improvement will accelerate clinical studies in Japan by entities in the world, which would results in the contribution to healthy life expectancy for people.
・CIN will also support for marketing in Asia of medial products developed in Japan.

National institute of Biomedical Innovation, Health and Nutrition
Hospitals in networks in Japan
Hospitals in Asia

・Acceleration of global clinical trials
・Asian Regulatory Training center
・Development of registries for patients with intractable diseases
・Rare diseases drug development Gateway

National Center, Clinical Research Core Hospital

・Development of disease registries
・Foundation of a clinical trial consortium, acceleration of clinical studies
・Advancement of regenerative medicine clinical studies
・Establishment of a Clinical Trial Cooperation Office

Participation in the consortium
Data provision (With consideration to personal information)

Industry

・Utilizes data in clinical studies
・Performs clinical studies quickly and cost-effectively

・Personnel exchanges
・Post marketing safety measures

・Support for R&D
・human resource cultivation in the clinical research and trial field

・Research for method to utilize disease registry in clinical study (Regulatory Science)

PMDA
Jurisdiction : MHLW

AMED
Jurisdiction : CAO, MEXT, MHLW, METI

CIN Promotion Conference
Composed of stakeholders , including National Centers, Industries and Japanese Government; and promotes the CIN project.

Activation of clinical studies in Japan by entities in the world

21

http://pari.u-tokyo.ac.jp/eng/event/smp150818_mori.pdf

Tripartite meeting of EMA/FDA/PMDA

- To accelerate development of antimicrobial agents
  - Regulatory convergence of regulatory requirements
  - Utilization of clinical trial networks
  - New flame works to collect data efficiently through product life cycle

Japanese Children Trials Network (JCTN)

- Established in November 2010
- Mainly consists of the member of the Japanese Association of Children's Hospitals and Related Institutions

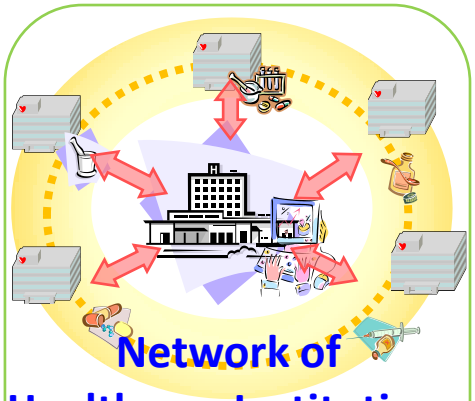
Efforts of the JCTN

- Centralization of administrative functions
- Establishment of Central IRB
- Education and training of member institutions
- Promotion of efficiency of clinical trials and infrastructure development
- Feasibility survey of clinical trials
- Making requests to pharmaceutical companies for cooperation in clinical trials conducted by physicians

Recent framework implemented by MHLW(1)
Project to improve the environment of use of medicines in children

Diagram made from http://www.mhlw.go.jp/sinsei/chotatu/chotatu/kikaku/2017/04/kk0406-01.html

Databases



Publications

Overseas information

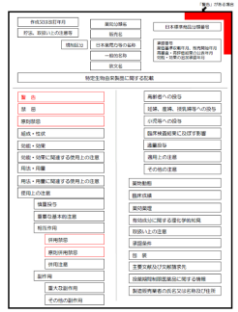
厚生労働省
Ministry of Health, Labour and Welfare

Commissioned

Collect and organize information

Evaluation by WG of experts

Partial change application



Revision of PI

Post report on website

Recent framework implemented by MHLW(2)

Medical Pediatric Breakthrough Program

Tentative title

国立研究開発法人 日本医療研究開発機構
Japan Agency for Medical Research and Development
AMED

**1 AMED Cyclic Innovation for Clinical Empowerment (CiCLE) Program

Promote pediatric medicines development in Japan

Research grant

**1

Funding loan

PS, PO Support

**1

Repayment after completion of the project (interest-free)

WG on development of pediatric medicines

Priority list

Japan Pediatric Society (JPS)

Develop a priority list on need for pediatric medicines by disease category

Secretariat to support multi-regional research (tentative title)**2

Collaborate as needed

Overseas clinical trials network

Domestic clinical trials network

Cooperate in the development of requested product

International joint research MRCT

PIP
PSP

Request

Sponsor

Drug approval

**2 Placed at National Center for Child Health and Development

Work together
for better anti-infective therapy
to paediatric population