独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

PMDA Public Workshop
"Role of Model Informed Drug Development"
March 24, 2021

Quantitative M&S and MIDD in PMDA: Activity and Perspective

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Office of New Drug IV/Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency (PMDA)

Biography

- I am Associate Senior Scientist for clinical pharmacology and pharmacokinetics at PMDA, Japan. I have over 10 years' experience reviewing the pharmacokinetics, clinical pharmacology and pharmacometrics of new drugs. From 2016 to 2017, I worked as ORISE Fellow for Division of Pharmacometrics, Office of Clinical Pharmacology/CDER/U.S.FDA. In PMDA, I am in charge of clinical pharmacology and pharmacometrics in the Modeling & Simulation project team. And, I contributed to develop Japanese pharmacometrics related guidelines including PBPK reporting guideline, Exposure-Response guideline and Population approach (PopPK, PopPK/PD) guideline.

Disclaimer

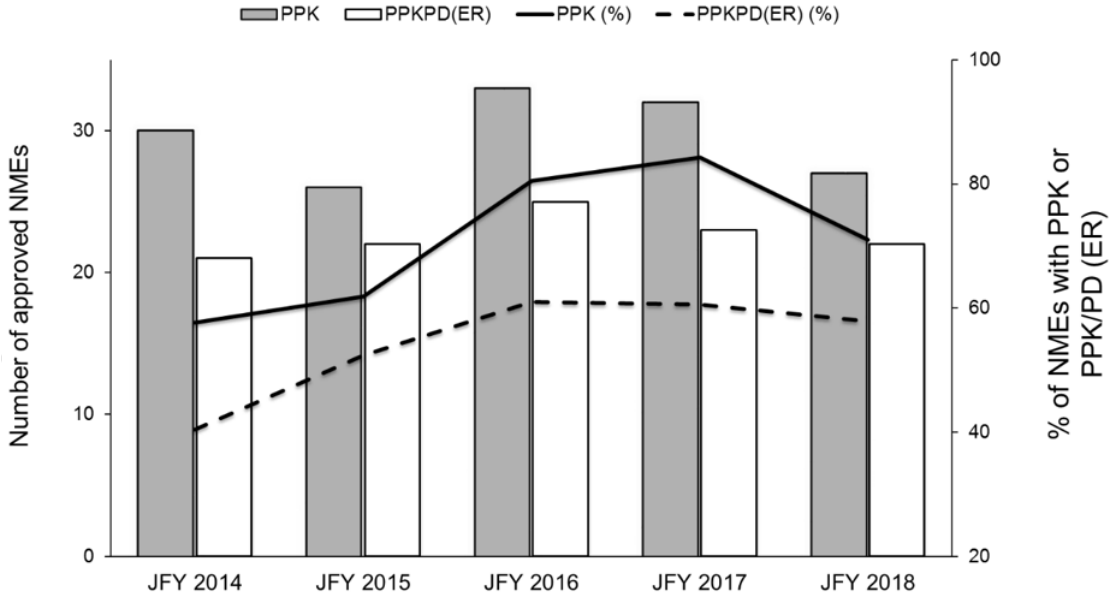
- The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA

Outline

- Current state of new drug review utilizing M&S in PMDA
- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
- Future prospects on Quantitative M&S : Perspective from Japanese regulatory agency

PPK and E-R(PPK/PD) in NDA submissions in Japan

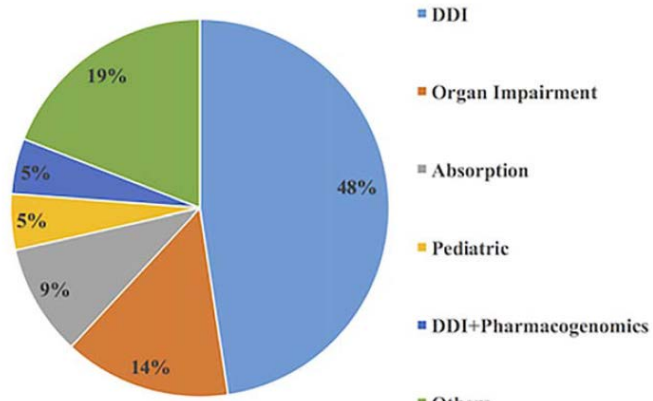
Trends of Pop approaches (PPK and PPK/PD (E-R)) in NMEs approved between 2014 and 2018



CPT Pharmacometrics Syst. Pharmacol. 2020 9(10) 550-552.

PBPK modeling submissions to the PMDA

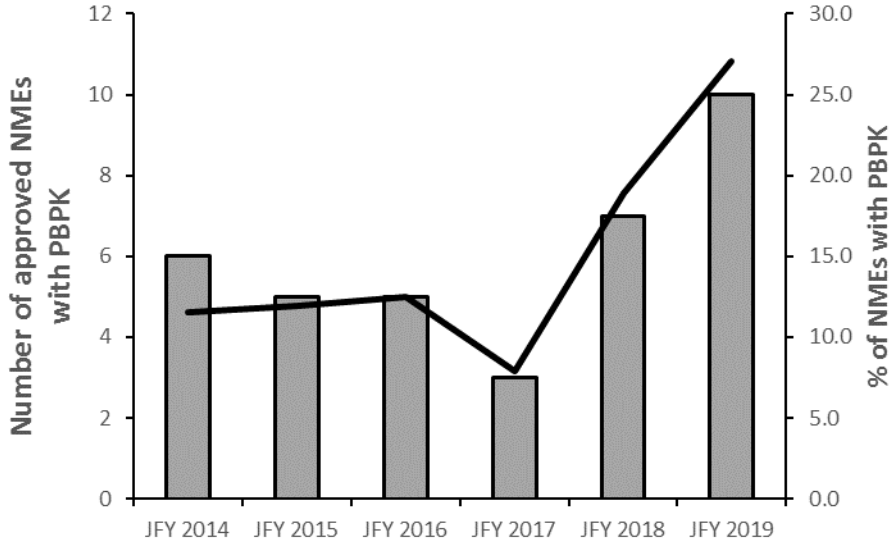
Between 2014 to 2016



17 cases

Figure 1 PBPK application in the 17 submissions in NDAs of NMEs received by the PMDA from 2014 to 2016. In some cases, multiple PBPK M&S reports were included in one submission.

CPT Pharmacometrics Syst. Pharmacol. 2017 6(7) 413-415.



From in-house database

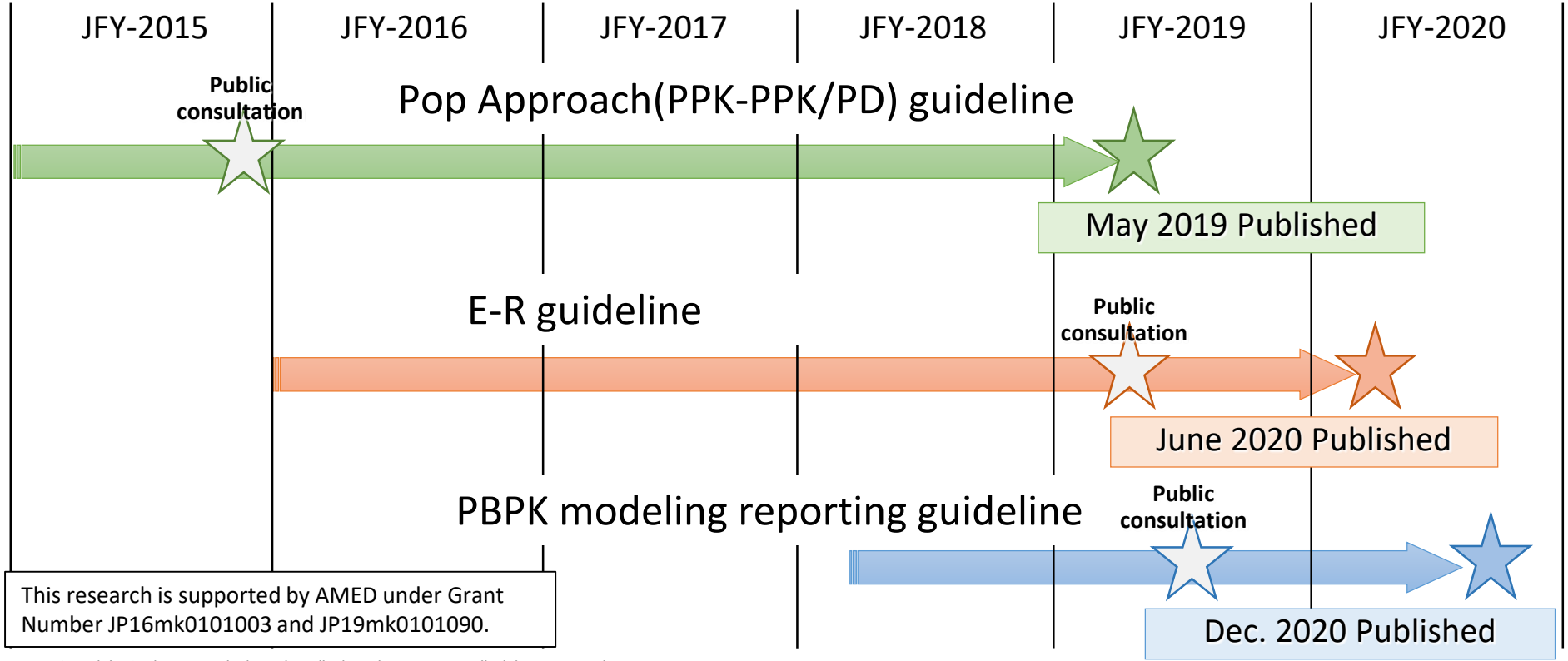
Outline

- Current state of new drug review utilizing M&S in PMDA
- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
- Future prospects on Quantitative M&S : Perspective from Japanese regulatory agency

Outline

- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
  - ☐ Developing Quantitative M&S related guidelines
  - ☐ M&S Project Team in PMDA
  - ☐ e-study data submission for regulatory review

Developing Quantitative M&S related guidelines in Japan



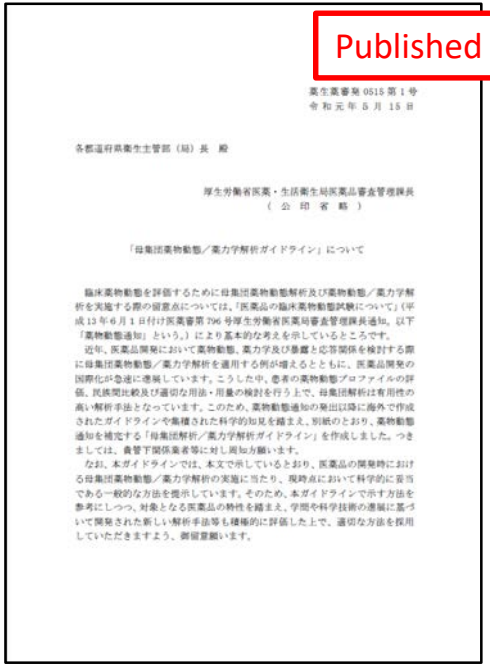
This research is supported by AMED under Grant Number JP16mk0101003 and JP19mk0101090.

Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis

Japanese(Original) version

English(for reference) version

Published on May 15, 2019



薬生薬審発 0515 第 1 号
令和 元 年 5 月 15 日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（ 公 印 省 略 ）

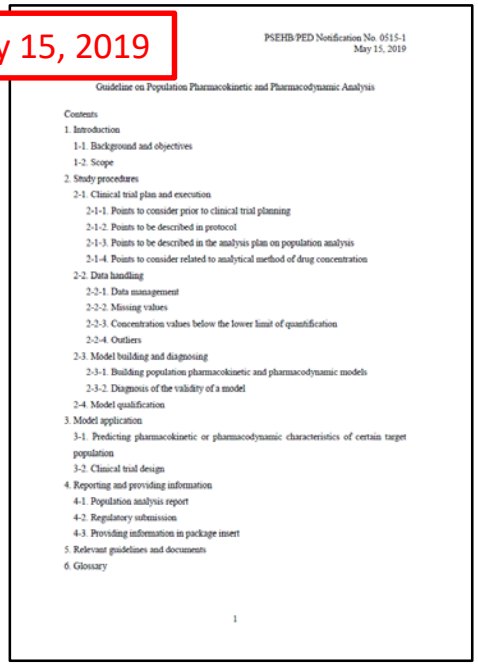
「母集団薬物動態／薬力学解析ガイドライン」について

臨床薬物動態を評価するために母集団薬物動態解析及び薬物動態／薬力学解析を実施する際の留意点については、「医薬品の臨床薬物動態試験について」（平成 13 年 6 月 1 日付け医薬審第 796 号厚生労働省医薬局審査管理課長通知。以下「薬物動態通知」という。）により基本的な考えを示しているところです。

近年、医薬品開発において薬物動態、薬力学及び暴露と応答関係を検討する際に母集団薬物動態／薬力学解析を適用する例が増えるとともに、医薬品開発の国際化が急速に進展しています。こうした中、患者の薬物動態プロファイルの評価、民族間比較及び適切な用法・用量の検討を行う上で、母集団解析は有用性の高い解析手法となっています。このため、薬物動態通知の発出以降に海外で作成されたガイドラインや集積された科学的知見を踏まえ、別紙のとおり、薬物動態通知を補完する「母集団解析／薬力学解析ガイドライン」を作成しました。つきましては、貴管下関係業者等に対し周知方願います。

なお、本ガイドラインでは、本文で示しているとおり、医薬品の開発時における母集団薬物動態／薬力学解析の実施に当たり、現時点において科学的に妥当である一般的な方法を提示しています。そのため、本ガイドラインで示す方法を参考にしつつ、対象となる医薬品の特性を踏まえ、学問や科学技術の進展に基づいて開発された新しい解析手法等も積極的に評価した上で、適切な方法を採用していただきますよう、御留意願います。

https://www.pmda.go.jp/files/000229625.pdf



PSEHB/PED Notification No. 0515-1
May 15, 2019

Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis

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2-1-3. Points to be described in the analysis plan on population analysis
2-1-4. Points to consider related to analytical method of drug concentration
2-2. Data handling
2-2-1. Data management
2-2-2. Missing values
2-2-3. Concentration values below the lower limit of quantification
2-2-4. Outliers
2-3. Model building and diagnosing
2-3-1. Building population pharmacokinetic and pharmacodynamic models
2-3-2. Diagnosis of the validity of a model
2-4. Model qualification
3. Model application
3-1. Predicting pharmacokinetic or pharmacodynamic characteristics of certain target population
3-2. Clinical trial design
4. Reporting and providing information
4-1. Population analysis report
4-2. Regulatory submission
4-3. Providing information in package insert
5. Relevant guidelines and documents
6. Glossary

1

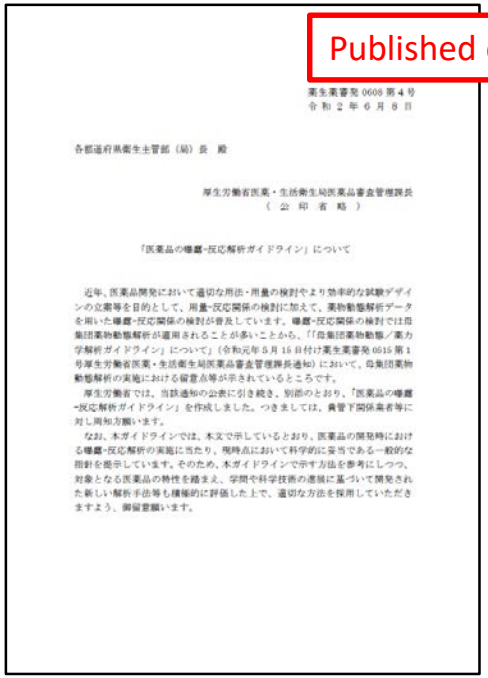
https://www.pmda.go.jp/files/000230073.pdf

Guideline for Exposure-Response Analysis of Drugs

Japanese(Original) version

English(for reference) version

Published on June 8, 2020



薬生薬審発 0608 第 4 号
令 和 2 年 6 月 8 日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（ 公 印 省 略 ）

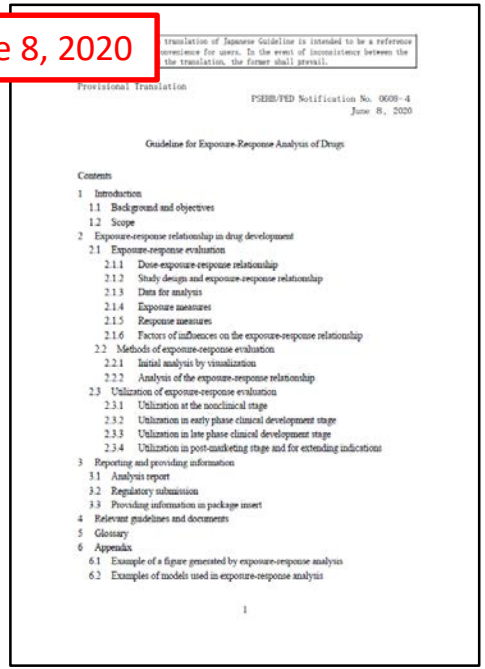
「医薬品の曝露-反応解析ガイドライン」について

近年、医薬品開発において適切な用法・用量の検討やより効率的な試験デザインの立案等を目的として、用量-反応関係の検討に加えて、薬物動態解析データを用いた曝露-反応関係の検討が普及しています。曝露-反応関係の検討では母集団薬物動態解析が適用されることが多いことから、「「母集団薬物動態／薬力学解析ガイドライン」について」（令和元年 5 月 16 日付け薬生薬審発 0515 第 1 号厚生労働省医薬・生活衛生局医薬品審査管理課長通知）において、母集団薬物動態解析の実施における留意点等が示されているところです。

厚生労働省では、当該通知の公表に引き続き、別添のとおり、「医薬品の曝露-反応解析ガイドライン」を作成しました。つきましては、貴管下関係者等に対し周知方願います。

なお、本ガイドラインでは、本文で示しているとおり、医薬品の開発時における曝露-反応解析の実施に当たり、現時点において科学的に妥当である一般的な指針を提示しています。そのため、本ガイドラインで示す方法を参考にしつつ、対象となる医薬品の特性を踏まえ、学問や科学技術の進展に基づいて開発された新しい解析手法等も積極的に評価した上で、適切な方法を採用していただきますよう、御留意願います。

https://www.pmda.go.jp/files/000235381.pdf



translation of Japanese Guideline is intended to be a reference convenience for users. In the event of inconsistency between the the translation, the former shall prevail.

Provisional Translation

PSEHB/PED Notification No. 0608－4
June 8, 2020

Guideline for Exposure-Response Analysis of Drugs

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1 Introduction
1.1 Background and objectives
1.2 Scope
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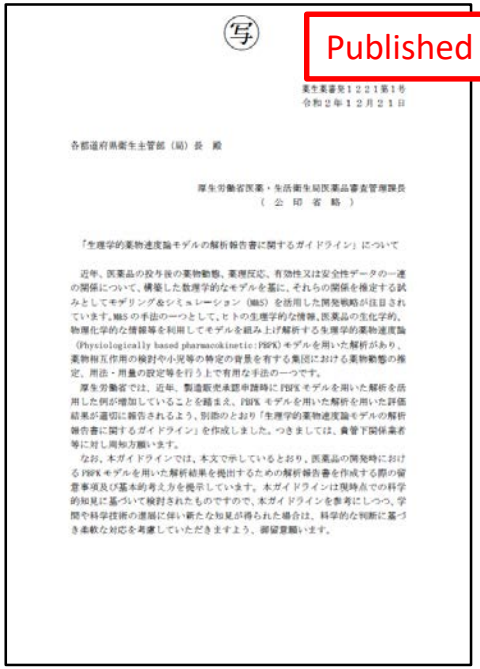
3.3 Providing information in package insert
4 Relevant guidelines and documents
5 Glossary
6 Appendix
6.1 Example of a figure generated by exposure-response analysis
6.2 Examples of models used in exposure-response analysis

1

https://www.pmda.go.jp/files/000235382.pdf

Guidelines for Analysis Reports Involving PBPK Models

Japanese(Original) version



薬生薬審発１２２１第１号
令和２年１２月２１日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（　公　印　省　略　）

「生理学的薬物速度論モデルの解析報告書に関するガイドライン」について

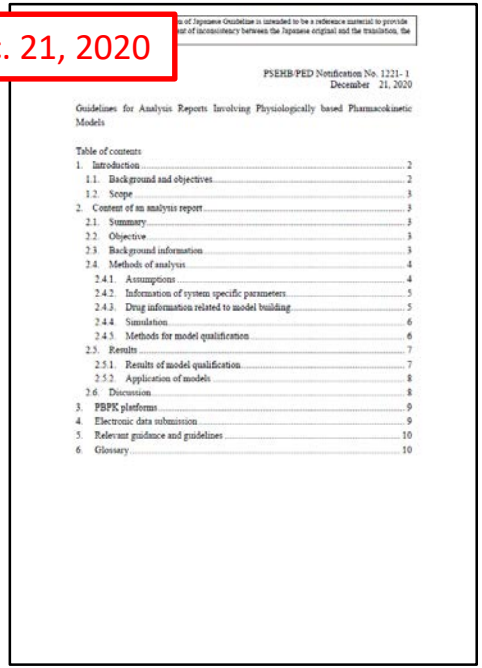
近年、医薬品の投与後の薬物動態、薬理反応、有効性又は安全性データの一連の関係について、構築した数理学的なモデルを基に、それらの関係を推定する試みとしてモデリング&シミュレーション（M&S）を活用した開発戦略が注目されています。M&Sの手法の一つとして、ヒトの生理学的な情報、医薬品の生化学的、物理化学的な情報等を利用してモデルを組み上げ解析する生理学的薬物速度論（Physiologically based pharmacokinetic：PBPK）モデルを用いた解析があり、薬物相互作用の検討や小児等の特定の背景を有する集団における薬物動態の推定、用法・用量の設定等を行う上で有用な手法の一つです。

厚生労働省では、近年、製造販売承認申請時にPBPKモデルを用いた解析を活用した例が増加していることを踏まえ、PBPKモデルを用いた解析を用いた評価結果が適切に報告されるよう、別添のとおり「生理学的薬物速度論モデルの解析報告書に関するガイドライン」を作成しました。つきましては、貴管下関係業者等に対し周知方願います。

なお、本ガイドラインでは、本文で示しているとおり、医薬品の開発時におけるPBPKモデルを用いた解析結果を提出するための解析報告書を作成する際の留意事項及び基本的考え方を提示しています。本ガイドラインは現時点での科学的知見に基づいて検討されたものですので、本ガイドラインを参考にしつつ、学問や科学技術の進展に伴い新たな知見が得られた場合は、科学的な判断に基づき柔軟な対応を考慮していただきますよう、御留意願います。

Published on Dec. 21, 2020

English(for reference) version



PSEHB/PED Notification No. 1221-1
December 21, 2020

Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

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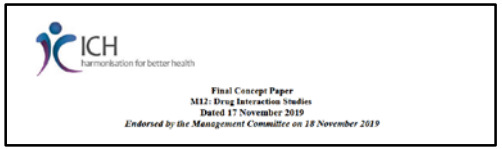
https://www.pmda.go.jp/files/000238191.pdf

https://www.pmda.go.jp/files/000238192.pdf

Other Guidelines

- ICH M12：Drug Interaction Studies


ICH harmonisation for better health

Final Concept Paper
M12: Drug Interaction Studies
Dated 17 November 2019
Endorsed by the Management Committee on 18 November 2019

https://database.ich.org/sites/default/files/M12_FinalConceptPaper_2019_1117.pdf

- ICH E11(R1)：Addendum to ICH E11: Clinical investigation of medicinal products in the pediatric population
- ICH E11A：Pediatric Extrapolation


INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

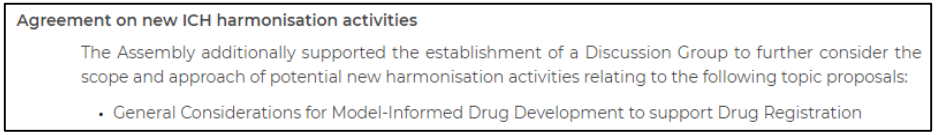
ICH harmonisation for better health

Final Concept Paper
Pediatric Extrapolation
3 October 2017
Endorsed by the Management Committee on 17 October 2017

Type of Harmonisation Action Proposed: New Efficacy Guideline under E11: E11A Clinical Investigation of Medicinal Products in the Pediatric Population

https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf
https://database.ich.org/sites/default/files/E11A_EWG_Concept_Paper.pdf

- ICH MIDD topic


Agreement on new ICH harmonisation activities

The Assembly additionally supported the establishment of a Discussion Group to further consider the scope and approach of potential new harmonisation activities relating to the following topic proposals:

- General Considerations for Model-Informed Drug Development to support Drug Registration

https://www.ich.org/pressrelease/ich-assembly-virtual-meeting-may-2020

Outline

- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
  - ☐ Developing Quantitative M&S related guidelines
  - ☐ M&S Project Team in PMDA
  - ☐ e-study data submission for regulatory review

M&S Project Team in PMDA

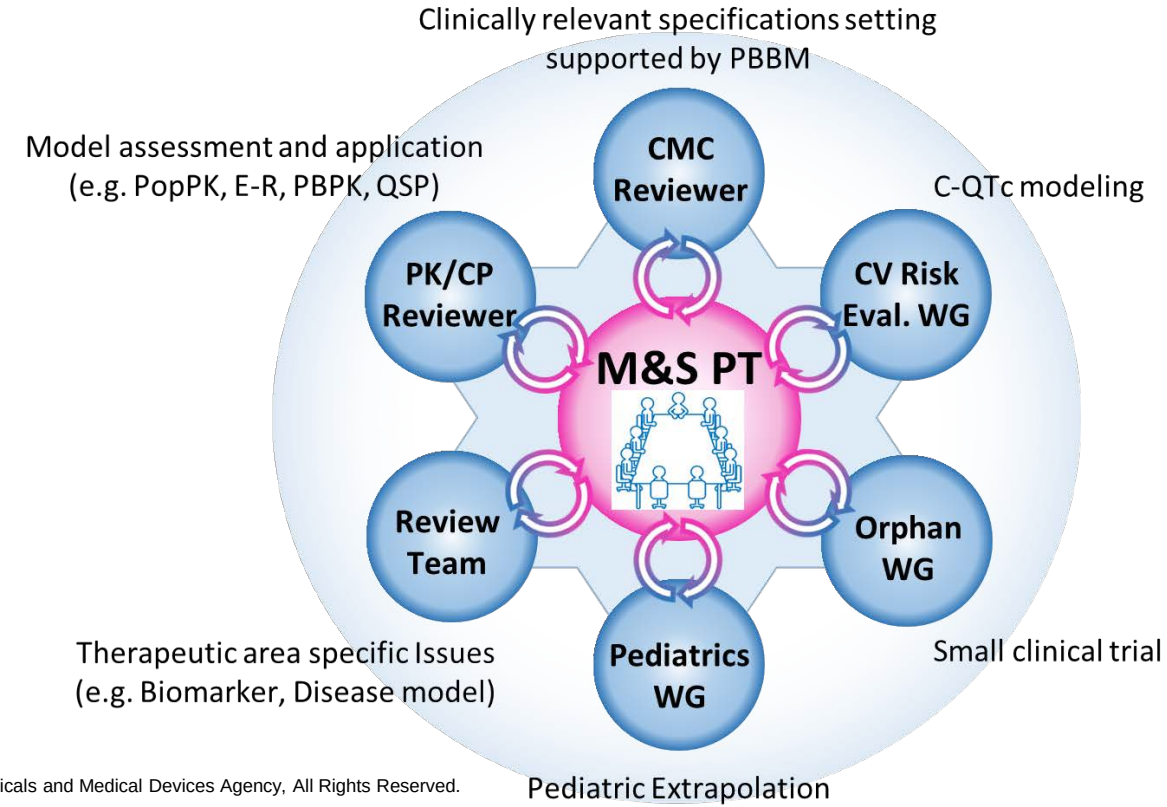
- Strengthening the review system for sharing and utilization of share and use of experiences/knowledge related to M&S

Framework to enable the discussion beyond expertise and therapeutic areas

- Discussion between Clinical Pharmacology/PK, Biostatistics, Clinical medicine, etc.
- Sharing the experiences/knowledge between the review teams
- Collaboration with other project teams in PMDA

- Scientific evaluation and decision making of M&S related issues in product review
- Sharing the information within PMDA and with other stakeholders
- Collaboration with other regulatory agencies

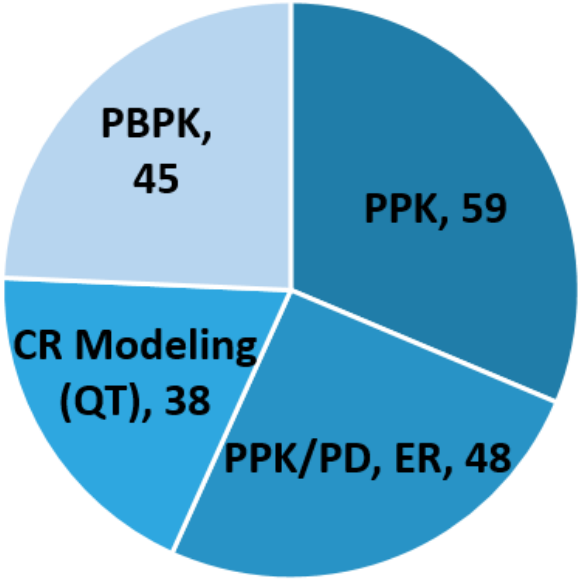
Collaborations with other project teams and reviewers



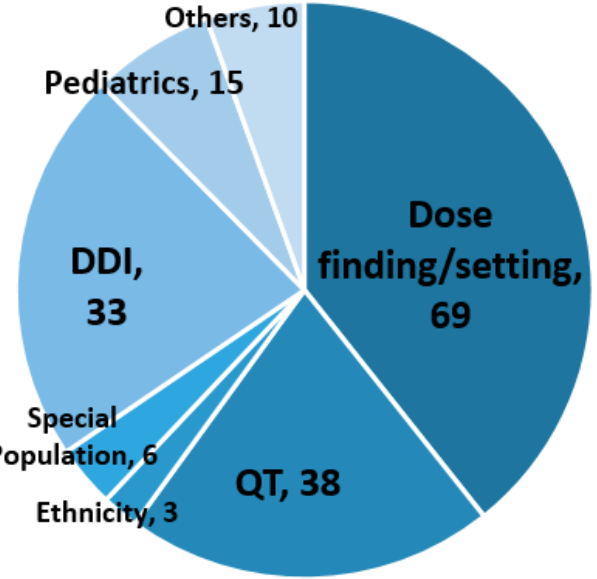
Number of contact from review team (Apr. 2016 to Feb. 2021)

Review or Consultation

Model type*



Objectives*

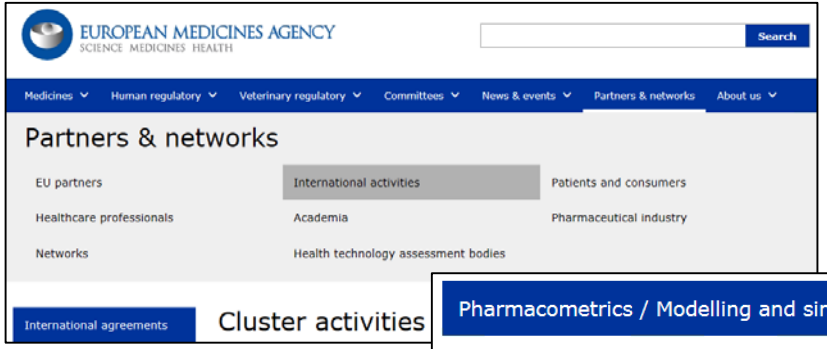


*Includes multiple cases

M&S Project Team in PMDA

International collaborations for M&S

Cluster activities on Pharmacometircs with EMA, FDA, HC and TGA



The European Medicines Agency (EMA) holds regular meetings by phone or videoconference with other non-EU regulators in so-called 'clusters'. The clusters are areas of cooperation focusing on special topics and therapeutic areas identified as requiring an intensified exchange of information and collaboration.

The type of information exchanged includes applications for marketing authorisation and extensions of indications, including risk-management plans and evaluation of safety signals.

The clusters were initially set up by EMA and United States (US) Food and Drug Administration (FDA). Other global regulators, including Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the Australian Therapeutic Goods Administration (TGA), now participate in some of the clusters.

In addition to regular cluster activities, ad-hoc product- or issue-related teleconferences are also held when required.

Pharmacometrics / Modelling and simulation

- Established: 2016
- Meeting frequency: quarterly by teleconference
- Participants: EMA, FDA, PMDA, Health Canada

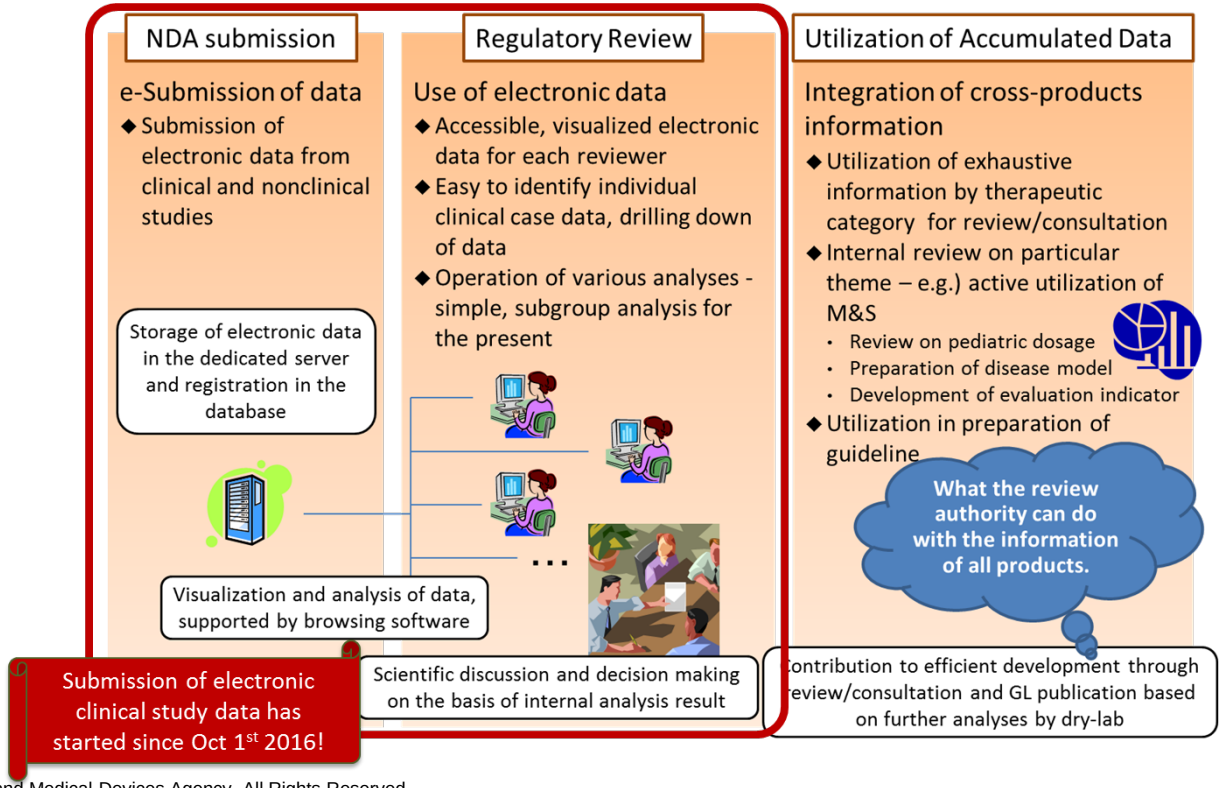
The objective of the cluster is to exchange information and perspectives on pharmacometrics, including guidelines, workshops, publications and products under parallel assessment. The Agencies will also work towards the harmonisation of their practices and activities in this area.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000655.jsp&mid=WC0b01ac0580953d98

Outline

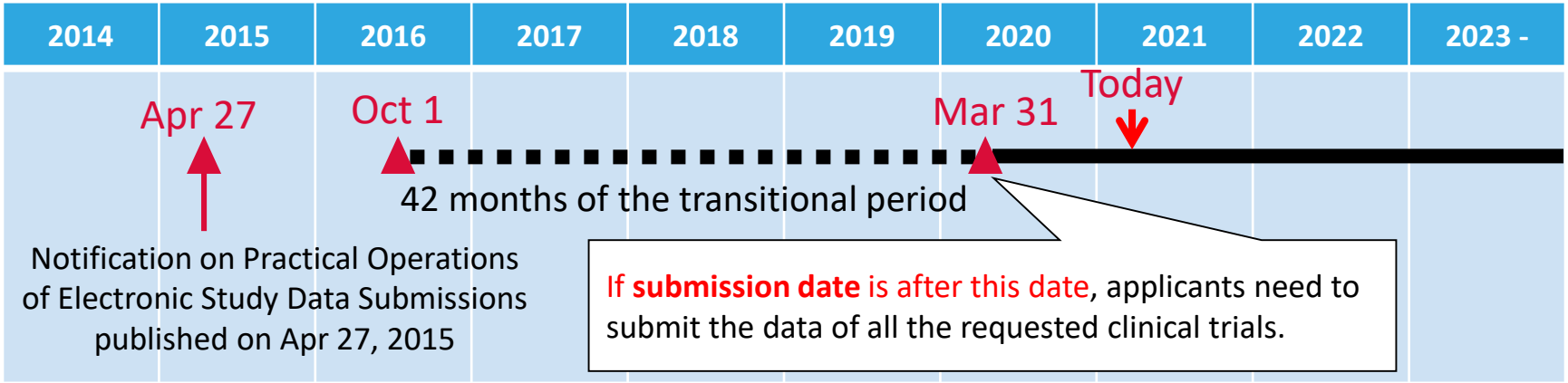
- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
  - ☐ Developing Quantitative M&S related guidelines
  - ☐ M&S Project Team in PMDA
  - ☐ e-study data submission for regulatory review

Accumulation and utilization of data



Transitional period is over…

- The transitional period was ended on March 31, 2020.
  - During the transitional period, applicants submitted the data of at least one clinical trial included in their clinical data packages.
  - After the period, applicants need to submit the data of all the requested clinical trials.



Electronic data to be submitted (for Clin. Pharm.)

<Standard two-stage analysis (NCA)>

- Datasets
  - SAS XPORT format (*.xpt)
  - ASCII Format Data Files
  - Phoenix Projects (*.phxproj)
  - WinNonlin Files (*.pmo, *.pwo) etc.
- Dataset definition documents
- Programs and others
  - Detailed information on the analyses

<PBPK modeling>

- Model information, Datasets as e-data
  - Files that contain information on the model structure used for the analysis
  - Clinical study datasets, including blood concentration data
- Dataset definition documents

<Population analysis (PPK, E-R etc.)>

- Datasets
  - SAS XPORT format (*.xpt)
  - ASCII Format Data Files etc.
- Dataset definition documents
- Programs
  - control files
  - Files into which major results are outputted
  - Files on simulation
  - Detailed information of the program procedures

Scientific discussion and decision making on the basis of internal analysis results.

Outline

- Current state of new drug review utilizing M&S in PMDA
- Modernization of the Clinical Pharmacology and Pharmacometric reviews in PMDA
- Future prospects on Quantitative M&S : Perspective from Japanese regulatory agency

Accumulation of e-study data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

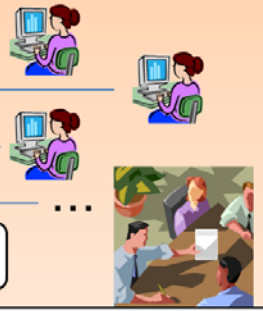
Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

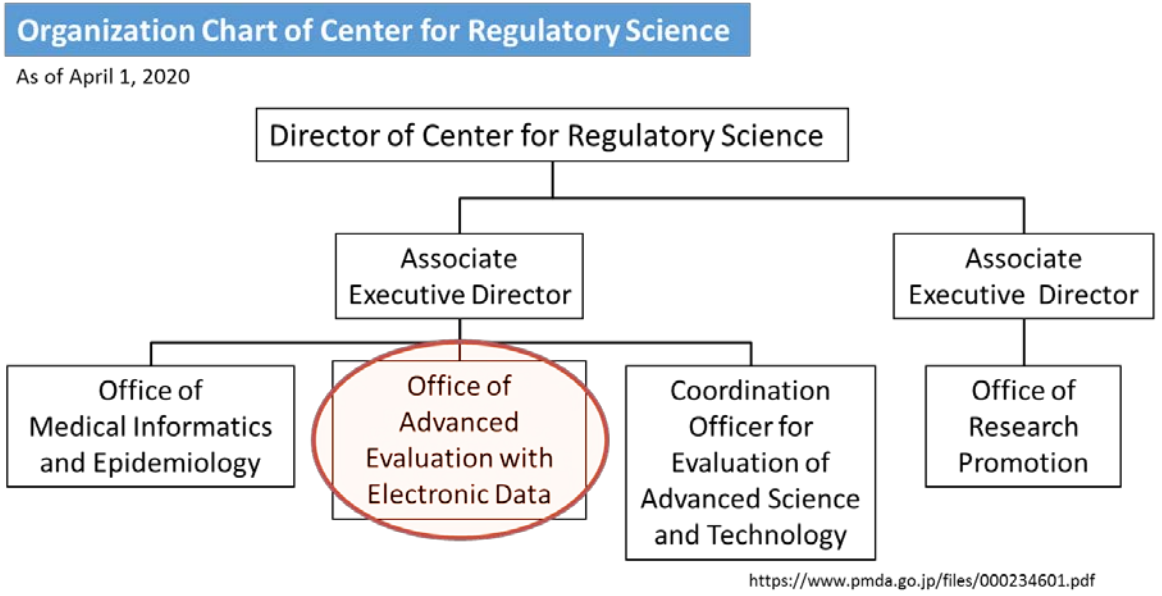
Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Center for Regulatory Science (Established on April 1, 2018)



"Office of Advanced Evaluation with Electronic Data" is a part of the Regulatory Science Center.

Examples of utilization of accumulated e-study data

- Accumulation and integration of exhaustive information about the drugs by therapeutic category or drug mechanism of action
  - Cross-product information of particular diseases (efficacy, safety, and placebo effects)
  - Cross-indication evaluation of drug safety
- Internal review on particular theme, e.g. M&S
  - Investigation of exposure-biomarker-clinical outcome
  - Similarity of exposure-clinical outcome relationship between populations
- Guidance development
  - Guidance for therapeutic areas and specific topics
  - Points to be considered of particular methodologies

Utilization of e-study data in the future

Utilization of study data for new drug review

- Improvement of predictability of efficacy and safety
- Reviewing M&S results
- Reviewing novel evaluation methods
- Swift and effective decision-making

- Data accumulation
- Experiences of data evaluation

Utilization of accumulated study data

- Information from cross-product analysis
- Active use of M&S
- Evaluation of innovative analysis methods based on the accumulated data
- Experiences of meta-analytic approach

Submission of standardized study data

- Consultation based on the cross-product information
- Guidance for therapeutic areas
- Issuance of points to considers for methodology

Efficient new drug development

- Use of consultation meeting based on the cross-product information by PMDA
- Active use of M&S
- Use of innovative and appropriate methods for the purpose

- Consultation/guidance about innovative analysis methods
- Contribution to data standardization

Use of various data sources in the future

- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources

Utilization of e-study data in the future

Utilization of study data for new drug review

- Improvement of predictability of efficacy and safety

- Data accumulation

Utilization of accumulated study data

- Information from cross-product analysis
- Active use of M&S

✓ Quantitative M&S approach:
One of the powerful tool for to address regulatory questions based on accumulated data and other data sources.

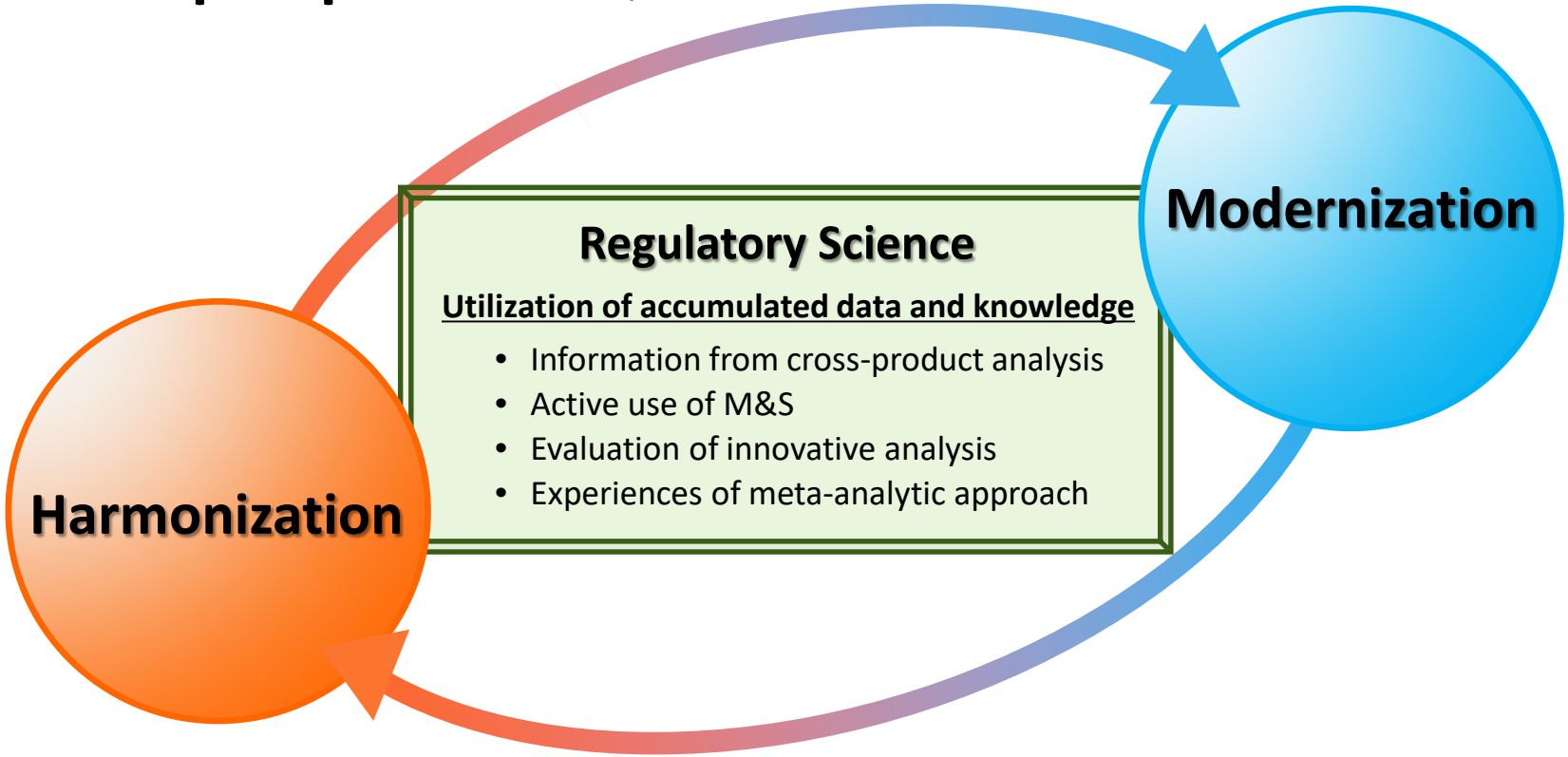
- Use of innovative and appropriate methods for the purpose

- Contribution to data standardization

Use of various data sources in the future

- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources

Future prospects on Quantitative M&S in PMDA



Conclusion

- Over the last two years, three guidelines have been published for important and basic modeling techniques in Japan.
- M&S PT supports to review on M&S and MIDD in PMDA, and M&S PT has experiences in over 100 cases.
- Quantitative M&S is useful for existing information including e-study data, and the integrated knowledge is expected to contribute to the efficiency of drug development.

Acknowledgments

- AMED and the AMED research group “Utilization of cross-product analyses of clinical study data and analyses of patient registry data for drug development”
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Pharmaceuticals and Medical Devices Agency

PMDA Public Workshop
“Role of Model Informed Drug Development”
March 24, 2021

Thank you