Current Status and Challenges of Model Informed Drug Development in Clinical Development in Japan

So Miyoshi
Clinical Evaluation Expert Committee,
Drug Evaluation Committee,
Japan Pharmaceutical Manufacturers Association

Speaker's biography

So Miyoshi, PhD

- Head of Clinical Pharmacology at Pfizer R&D Japan since 2015.
- More than 20 years of experience in the application of quantitative clinical pharmacology and pharmacometrics for clinical development and new drug application (NDA) work not only for Japan but also for US, Europe, China and Korea as Global Clinical Pharmacology Lead and Pharmacometrician.
- PhD degree in Pharmaceutical Science at Kyushu University in 2008 (Prof. Shun Higuchi's Lab).
- Leader of the Clinical Pharmacology Task Force in the Japan Pharmaceutical Manufacturers Association (JPMA) from 2015 to 2020.
- Board of Directors of the International Society of Pharmacometrics (ISoP), effective January 1, 2021. http://go-isop.org/board-of-directors/

Today's Topics

- **Recent Activity of JPMA to Promote MIDD**
- **Case Studies**

  Does the M&S GLs promote the implementation of MIDD in Japan?
- **Bring Models to Patients**

  Model Informed Precision Dosing (MIPD)

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About JPMA

- The Japan Pharmaceutical Manufacturers Association (JPMA) is a voluntary association comprising 73 research-oriented pharmaceutical companies (as of January, 2021)
- JPMA, celebrating its 50th anniversary in 2018, has been contributing to advancing global healthcare through the development of innovative ethical drugs, facilitating sound development of the pharmaceutical industry through proactively establishing policies and recommendations in response to globalization and enhancing public understanding of pharmaceuticals

About JPMA: http://www.jpma.or.jp/english/about_us/about_us.html

About JPMA

- As a member of the IFPMA, JPMA is engaged with various global issues in the pharmaceutical and healthcare sector, including countermeasures against emerging diseases across the globe and infectious diseases in developing countries, drug access problems, intellectual property rights and the threat of counterfeit drugs
- Working collaboratively with PhRMA and EFPIA, JPMA takes active roles at ICH, which aims at international harmonization of pharmaceutical regulations
- Through mutual information sharing and close collaboration with each member organization, JPMA continues to act globally for the advancement of medical treatments for patients worldwide

Recent Activity of JPMA to Promote MIDD

- ICH activities
  - ✓ E11A EWG pediatric extrapolation
  - ✓ M12 EWG drug interaction – PBPK modeling
  - ✓ MIDD DG
- Collaboration with PMDA to open “Clinical Pharmacology Roundtable Discussion Forum”
  - ✓ The 1st roundtable discussion (PMDA, industry and academia) was held on Feb. 17, 2020
  - ✓ Theme: implementation of MIDD
  - ✓ Topics: application of MIDD in oncology, and in pediatric patients; education and organization to promote MIDD

Recent Activity of JPMA to Promote MIDD

- Contribution to prepare a set of three PMDA/MHLW guidelines for modeling and simulation in clinical development
  - ✓ Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis (May., 2019)
  - ✓ Guideline for Exposure-Response Analysis of Drugs (Jun., 2020)
  - ✓ Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models (Dec., 2020)
- Introduction and discussion on the guidelines at the annual scientific meeting of the Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) with regulatory agency and academia
- Preparation of a user's guide of "Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis" as JPMA internal document

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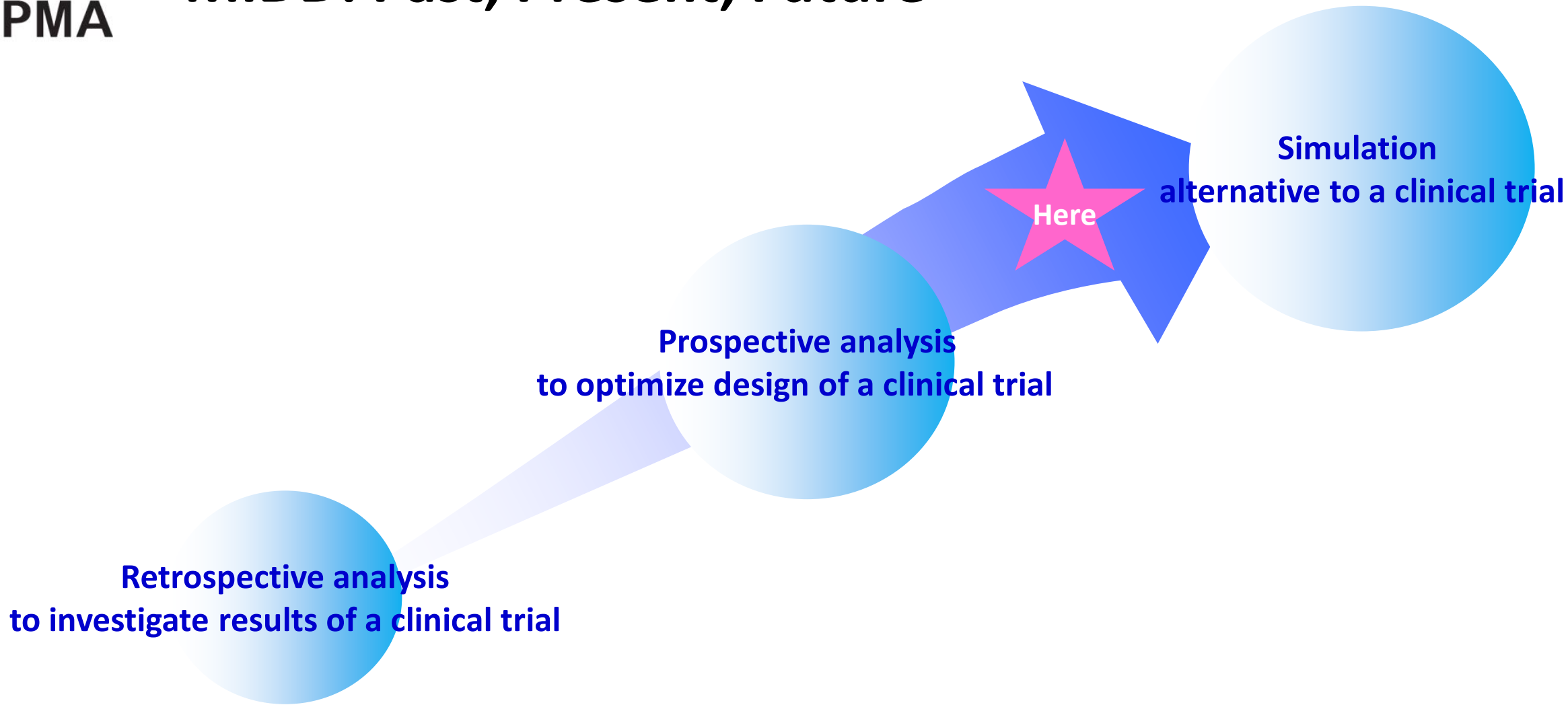
Guideline for Exposure-Response Analysis of Drugs (2020)

1 Introduction, 1.1 Background and objectives

- ✓ In drug development, **investigation of the relationship between exposure and response**, in addition to investigation of the relationship between dose and response (mainly efficacy or safety), is important to obtain useful information to determine the dosage and administration more efficiently in clinical studies at each stage of development, to build the study design, and to provide information to those involved in clinical practice.
- ✓ In recent years, it is expected that analyses of the exposure-response relationship and subsequent simulations of clinical responses based on results of the analyses will contribute to **improve the likelihood of success in confirmatory studies** in various disease areas.
- ✓ In addition, it is expected that exposure-response analyses will be further utilized as one of the methods for **estimating the proper dosage and administration** from limited clinical study results, as well as **avoiding the conduct of unnecessary clinical studies** for the development of medicinal products targeted for populations and diseases for which clinical studies are not feasible, as represented in children and orphan diseases.

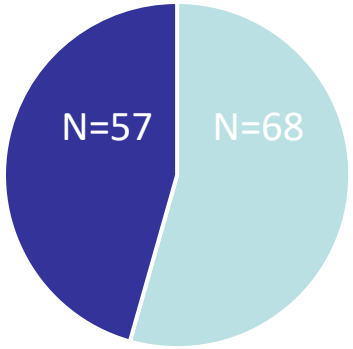
- **It is worthwhile to investigate an exposure-response relationship (PK-PD) integrating non-clinical and clinical data**
- **Simulation data has the same value as observed data**
- **It is possible to obtain approval of the dosage and administration which has not been investigated in a clinical study**

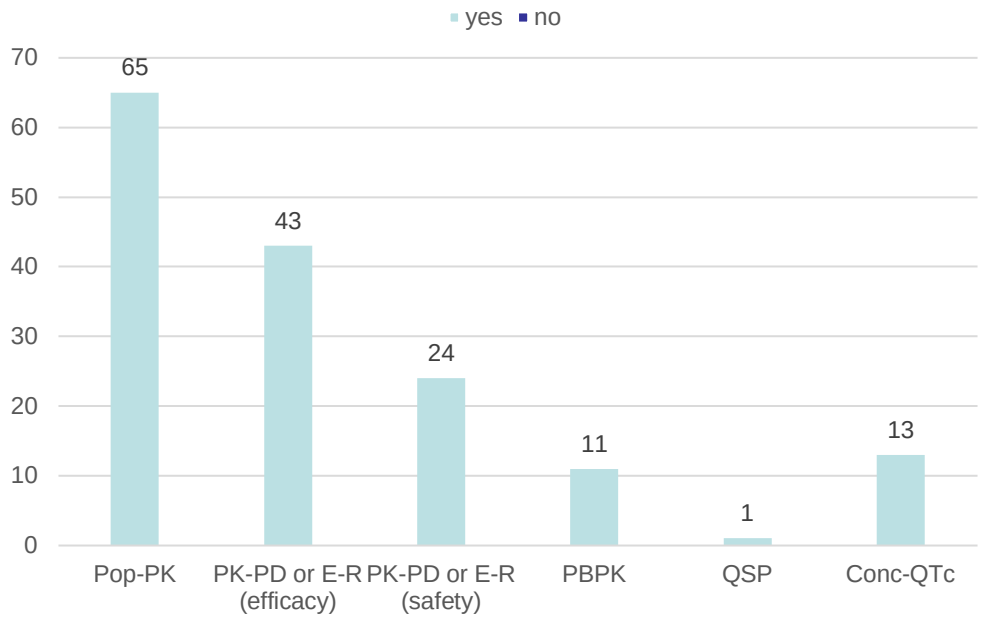
MIDD: Past, Present, Future



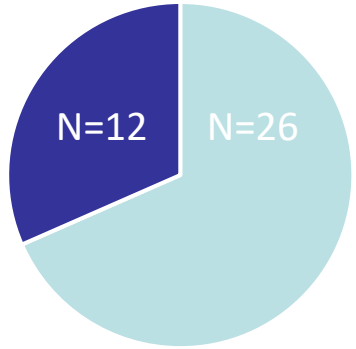
Trend of Modeling and Simulation J-NDA/J-sNDA in 2020

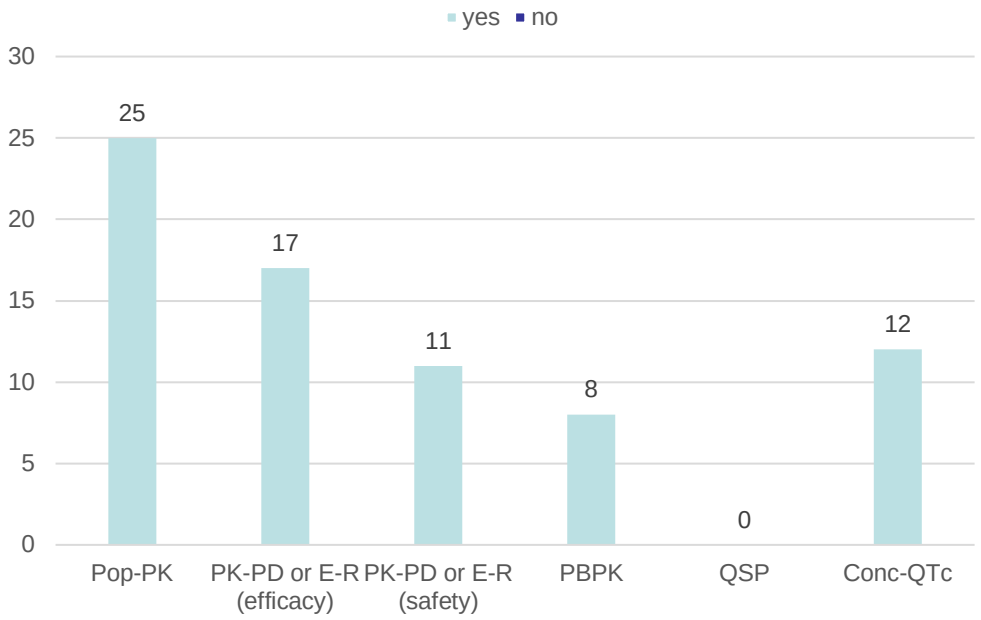
Was M&S described in CTD or PMDA review report?
(total number of NDA and sNDA = 125)





Was M&S described in CTD or PMDA review report?
(total number of NDA = 38)





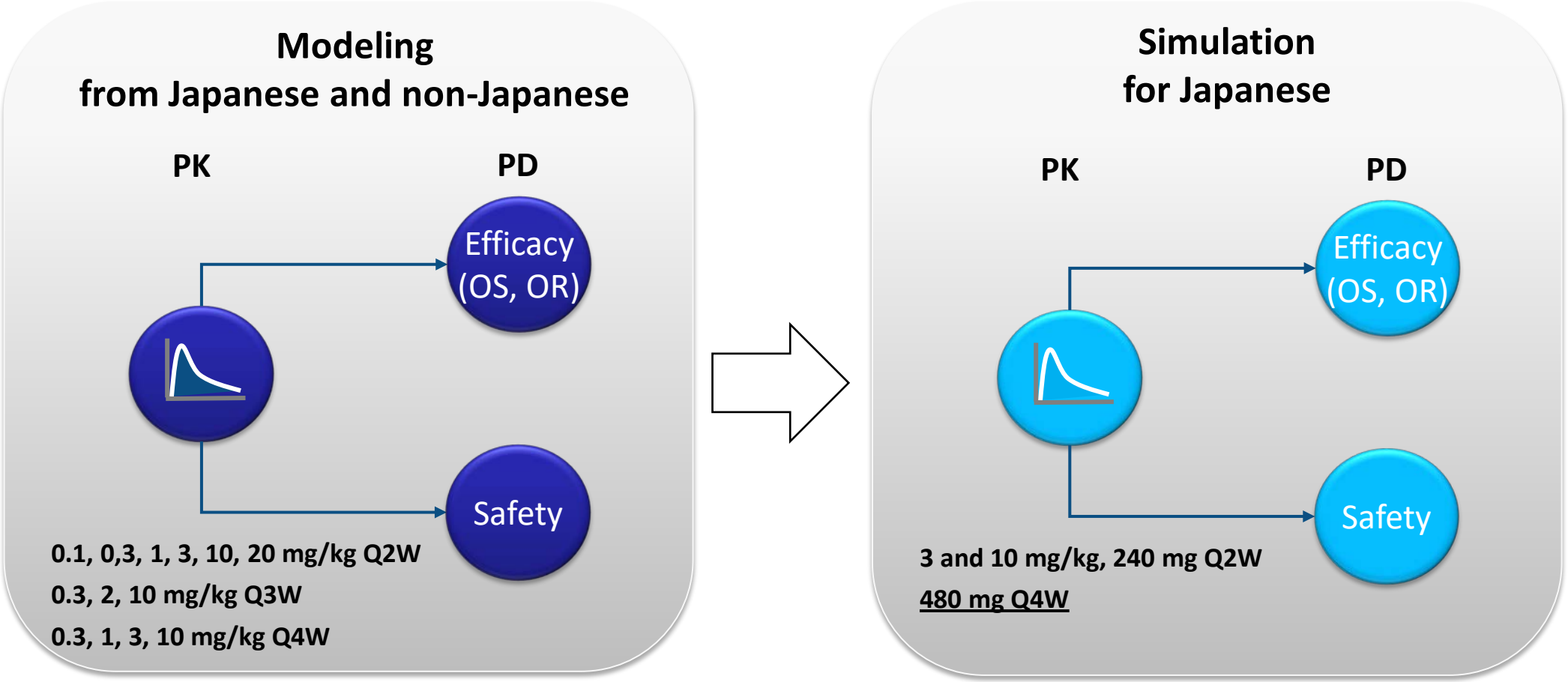
PMDA 医療用医薬品 情報検索: https://www.pmda.go.jp/PmdaSearch/iyakuSearch/

Case #1 OPDIVO® (nivolumab): New Dosing Regimen

- Background
  - ✓ Nivolumab (NIVO) is a fully human IgG4 antibody that targets the programmed death 1 immune checkpoint that provides survival benefits in patients with multiple tumor types
  - ✓ Flat dosing regimens of NIVO 240 mg every 2 weeks (Q2W) and 480 mg every 4 weeks (Q4W) are approved in the US, EU and several other markets
  - ✓ In Japan, NIVO 240 mg Q2W is approved for multiple tumor types following the approval of 3 mg/kg Q2W
- Application of MIDD
  - ✓ To assess the benefit-risk of NIVO 480 mg Q4W in Japanese patients using a model-base approach by leveraging robust characterization of NIVO pharmacokinetics and E-R relationships for efficacy and safety

Mayu Osawa et al., ACoP11, THU-055 (2020)
オプジーボ審査報告書（令和2年8月26日）: https://www.pmda.go.jp/drugs/2020/P20201002001/180188000_22600AMX00768_A100_1.pdf

Case #1 OPDIVO® (nivolumab): New Dosing Regimen



Mayu Osawa et al., ACoP11, THU-055 (2020)
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Case #1 OPDIVO® (nivolumab): New Dosing Regimen

- PK Exposure Comparisons in Japanese Patients
  - ✓ Population PK analysis was conducted using data from 24 clinical trials in and outside Japan
  - ✓ The data from 420 Japanese patients were used for exposure comparison
    - ➢ Cavg, ss for 480 mg Q4W was similar to that for 240 mg Q2W
    - ➢ Cmin, ss for 480 mg Q4W was lower than that for 240 mg Q2W, but, higher than Cmin, ss for 3 mg/kg Q2W
    - ➢ Cmax, ss for 480 mg Q4W was higher than that for 240 mg Q2W, but, lower than Cmax, ss for 10 mg/kg Q2W in which tolerability was observed in Japanese patients

Table 2 Predicted pharmacokinetc parameter of nivolumab in Japanese patients

Dose	C_{max1} (μg/mL)	$C_{avg,d28}$ (μg/mL)	$C_{min,d28}$ (μg/mL)	$C_{max,ss}$ (μg/mL)	$C_{avg,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)
3 mg/kg Q2W	50.9 (21.3)	30.8 (21.5)	26.6 (26.6)	113 (26.4)	76.3 (33.2)	59.6 (38.9)
240 mg Q2W	72.6 (21.9)	43.7 (20.6)	37.8 (26.9)	161 (27.5)	108 (34.7)	84.7 (40.9)
480 mg Q4W	145 (21.9)	52.9 (21.7)	28.3 (31.7)	218 (24.3)	108 (34.7)	67.6 (46.7)
10 mg/kg Q2W	186 (16.1)	119 (14.8)	103 (15.8)	412 (16.8)	287 (18.0)	226 (19.4)

Geometric mean (%CV)

Mayu Osawa et al., ACoP11, THU-055 (2020)
オプジーボ審査報告書（令和2年8月26日）: https://www.pmda.go.jp/drugs/2020/P20201002001/180188000_22600AMX00768_A100_1.pdf

Case #1 OPDIVO® (nivolumab): New Dosing Regimen

- Comparisons of Predicted Efficacy in Japanese Patients
  - ✓ E-R efficacy (OS and OR) using an exposure measure $C_{avg,d28}$ shows that the predicted efficacy profile is similar among the dosing regimens

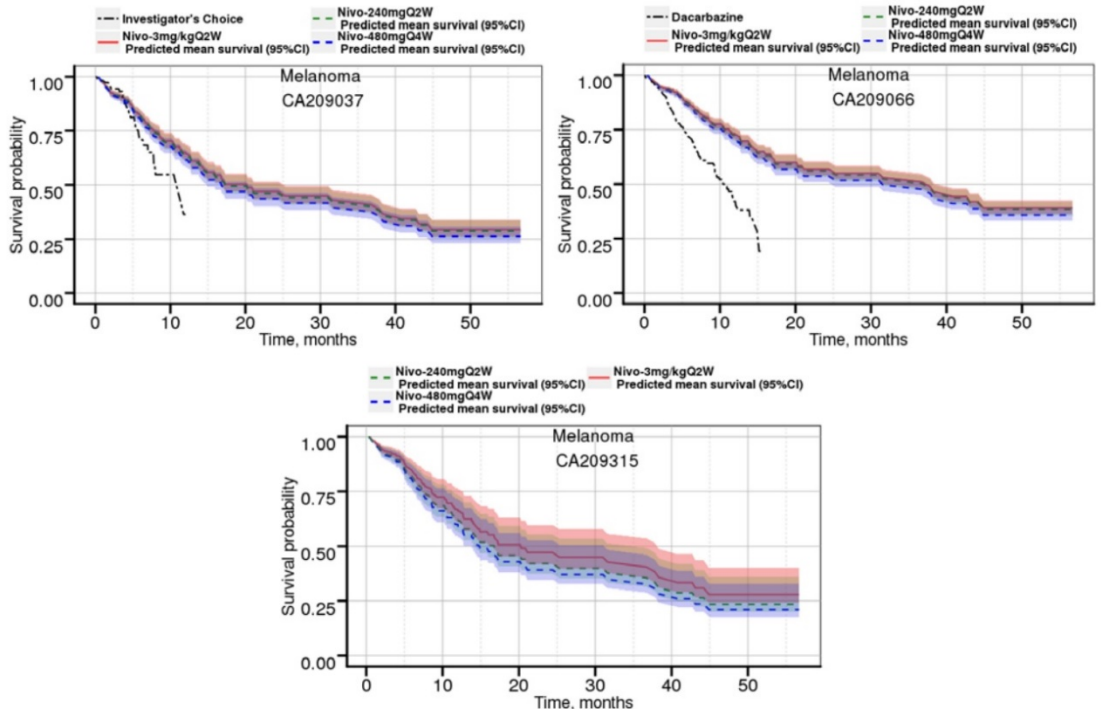

Figure 1. Predicted Mean Survival (95% CI) Using $C_{avg,d28}$ in Japanese Patients

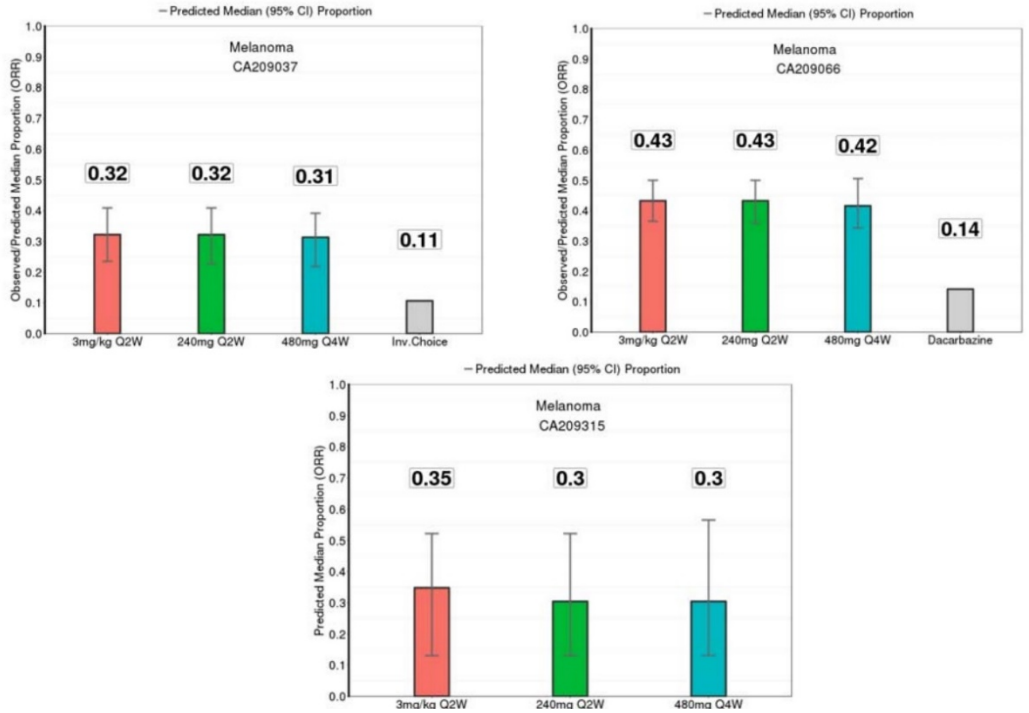

Figure 2. Predicted Median ORR Using $C_{avg,d28}$ in Japanese Patients

Mayu Osawa et al., ACoP11, THU-055 (2020)
オプジーボ審査報告書（令和2年8月26日）: https://www.pmda.go.jp/drugs/2020/P20201002001/180188000_22600AMX00768_A100_1.pdf

Case #1 OPDIVO® (nivolumab): New Dosing Regimen

- Comparisons of Predicted Safety in Japanese Patients
  - ✓ E-R safety using an exposure measure $C_{avgd,28}$ shows that the predicted safety profile is similar among the dosing regimens

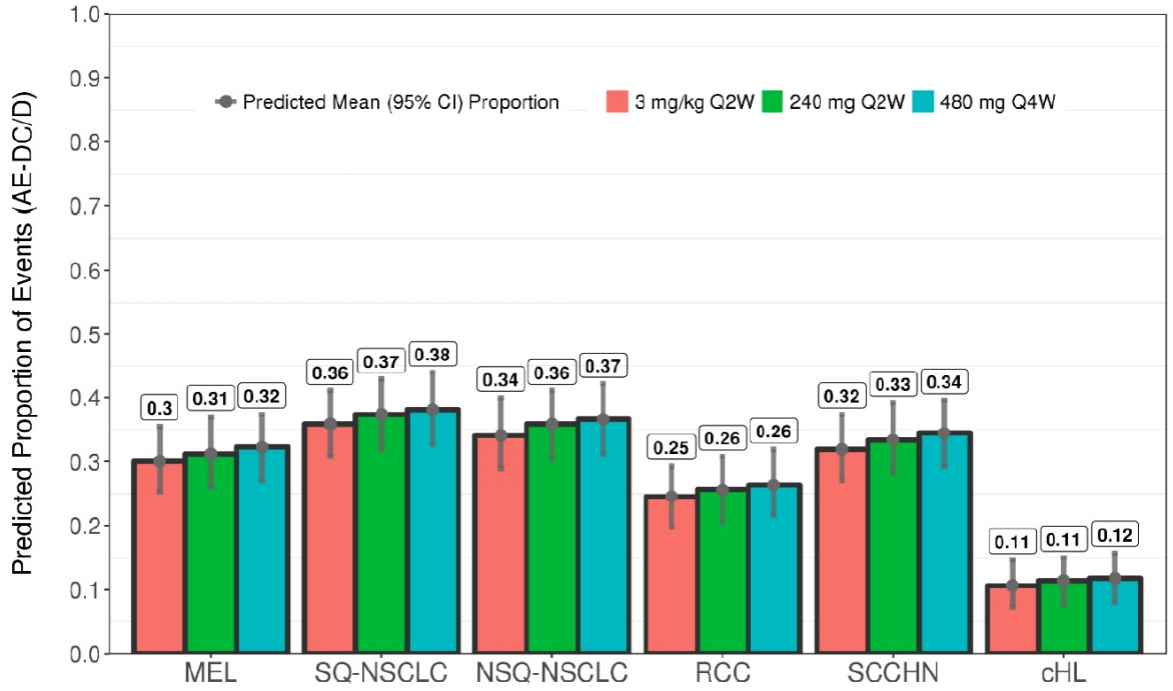

Figure 3. Model Predicted Proportion of AE-DC/D by Tumor Type in Japanese Patients

Mayu Osawa et al., ACoP11, THU-055 (2020)
オプジーボ審査報告書（令和2年8月26日）: https://www.pmda.go.jp/drugs/2020/P20201002001/180188000_22600AMX00768_A100_1.pdf

Case #1 OPDIVO® (nivolumab): New Dosing Regimen

- Summary
  - ✓ Modeling and simulation showed that the less frequent dosing regimen of NIVO Q4W is expected to produce a similar benefit-risk profile compared to the approved Q2W regimens, and has been approved as an alternative treatment for Japanese Patients
  - ✓ The evidence presented herein was the basis for the 480 mg Q4W approval in Japan
  - ✓ Those information were summarized in the package insert
    - ➢ Section 16.1.3 Population PK analysis
    - ➢ Section 16.8 Others – Exposure-Response analysis for efficacy and safety

Mayu Osawa et al., ACoP11, THU-055 (2020)
オプジーボ審査報告書（令和2年8月26日）: https://www.pmda.go.jp/drugs/2020/P20201002001/180188000_22600AMX00768_A100_1.pdf

Case #2 DAYVIGO® (lemborexant): Drug-Drug Interaction

- Background
  - ✓ DAYVIGO is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
  - ✓ The recommended dosage of DAYVIGO is 5 mg taken no more than once per night, immediately before going to bed
  - ✓ The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability
- Application of MIDD
  - ✓ To investigate the effect of weak CYP3A4 inhibitors on DAYVIGO by PBPK model

DAYVIGO米国添付文書: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf
デエビゴ審査報告書（令和元年11月19日）: https://www.pmda.go.jp/drugs/2020/P20200203001/170033000_30200AMX00017_A100_1.pdf

Case #2 DAYVIGO® (lemborexant): Drug-Drug Interaction

- Labeling in the US

2.2 Dosage Recommendations for Concomitant Use with CYP3A Inhibitors or CYP3A Inducers

Co-administration with Weak CYP3A Inhibitors

The maximum recommended dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

12.3 Pharmacokinetics

Drug Interaction Studies

Physiologically-based pharmacokinetic (PBPK) modeling predicted that concomitant use of weak CYP3A inhibitors increased lemborexant exposure by less than 2-fold.

- Japan Package Insert

✓ No information on the effect of weak CYP3A4 inhibitors on DAYVIGO

DAYVIGO米国添付文書: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf
デエビゴ審査報告書（令和元年11月19日）: https://www.pmda.go.jp/drugs/2020/P20200203001/170033000_30200AMX00017_A100_1.pdf

Case #2 DAYVIGO® (lemborexant): Drug-Drug Interaction

- Review Report　6.R.3

  (Applicant Company)

  - ✓ Simcyp version 17.1 was used to evaluate inhibition effect of weak CYP3A4 inhibitors on the PK of study drug. When model building, predictive check was performed using data from Phase I study, DDI study, and Food Effect study.
  - ✓ As a result of model verification used observed data from concomitant use with CYP3A4 inhibitors (itraconazole and fluconazole) or a CYP inducer (rifampicin), as shown in Table 31 listed predictive and observed C_{max} and $AUC_{0\text{-}t}$ of unchanged drug at a dose of 10 mg of the study drug, the model was determined to be appropriate.

Table 31 Predicted and observed C_{max} and $AUC_{0\text{-}t}$ of unchanged lemborexant following 10 mg dose

	AUC (concomitant/alone)		C_{max} (concomitant/alone)	
	Observed value	Predicted value	Observed value	Predicted value
itraconazole	3.58	3.11	1.36	1.39
fluconazole	3.76	2.83	1.62	1.37
rifampicin	0.033	0.19	0.085	0.38

DAYVIGO米国添付文書: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf
デエビゴ審査報告書（令和元年11月19日）: https://www.pmda.go.jp/drugs/2020/P20200203001/170033000_30200AMX00017_A100_1.pdf

Case #2 DAYVIGO® (lemborexant): Drug-Drug Interaction

- Review Report 6.R.3 (Continued from previous page)

（PMDA）

With regard to concomitant use with weak CYP3A4 inhibitors, PMDA commented:

- ✓ According to the applicant company, as predicted $AUC_{0\text{-}t}$ of the study drug alone was 1.77-fold relative to concomitant dose with a weak CYP3A4 inhibitor (fluoxetine) from PBPK model, recommended dose of the study drug with weak CYP3A4 inhibitors is 5 mg only.
- ✓ However, inhibition strength varies among weak CYP3A4 inhibitors. In Global (non-Japanese) Phase II study, the study drug was administered up to 25 mg/day and only one SAE (grand mal convulsion) occurred. In up to 20 mg/day where no SAE was observed, the dose dependent AE was somnolence only. The study drug can be promptly reduced if somnolence was observed.
- ✓ Based on the above, PMDA thinks the dosage of the study drug concomitant with weak CYP3A4 inhibitors is to be 5 mg and when there is no safety issues, it is to be subsequently increased to 10 mg.

DAYVIGO米国添付文書: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf
デエビゴ審査報告書（令和元年11月19日）: https://www.pmda.go.jp/drugs/2020/P20200203001/170033000_30200AMX00017_A100_1.pdf

Case #2 DAYVIGO® (lemborexant): Drug-Drug Interaction

- Summary
  - ✓ Although the reliability of PBPK modeling was agreed, the regulatory decision was different between FDA and PMDA

DAYVIGO米国添付文書: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf
デエビゴ審査報告書（令和元年11月19日）: https://www.pmda.go.jp/drugs/2020/P20200203001/170033000_30200AMX00017_A100_1.pdf

Case #3 XELJANZ® XR (tofacitinib): New Formulation, Extended-Release Tablet

Traditional Approach to register a modified release product

Clinical Efficacy Trial

Bioavailability Trials

FDA

MIDD Approach: PK/PD Bridge

PK/PD Bridge

- PK-PD well understood
- Predicted equi-efficacious
- Safety assured (equivalent or lower concentrations)
- No Efficacy Trial

Bioavailability Trials

FDA

RA: Marketed >1 year sooner

S. Marshall, Population Approach Group in Japan (PPK研究会) , 2018

Guideline for Exposure-Response Analysis of Drugs (2020)

2.3.4 Utilization in post-marketing stage and for extending indications

✓ …**sharing the reliable exposure-response model** that was established during the course of drug development with healthcare professionals appropriately is expected to greatly contribute to the **promotion of proper use of drug and personalized medicine in clinical settings**.

Case #2 DAYVIGO PBPK

✓ In drug development for a new formulation or an extension of indications in the post-marketing stage, the exposure-response model may presumably be applied (but are not limited) to the following purposes.

- To make it possible reliably to predict clinical response at any doses or exposure within the range of dose or exposure to be studied and thus **to set the dose or exposure range to be expected no clinical relevant difference or requiring adjustment of dosage and administration**.

Case #2 DAYVIGO PBPK

- To predict clinical response based on the simulated exposure under the **new dosage of new formulations developed for pediatric or for modified release etc**. and the **new dosage and administration** developed in the post-marketing stage.

Case #1 OPDIVO 480 mg Q4W

Case #3 XELJANZ ER tablet

For acceleration of MIDD in Japan: Comments from Industry

- Raise awareness of MIDD for all personnel besides ADME, CP, and PMx, and stakeholders in both of PMDA/MHLW and Pharmaceutical Industry
- Establish if there are any conflicts between newly issued M&S guidelines and existing guidelines regarding PMDA review process
- Utilize the Clinical Pharmacology Round Table: PMDA/MHLW, Industry (and Academia) to proactively discuss M&S and MIDD
- Discuss fully about M&S and MIDD at a PMDA consultation
- Place a new system for proactive discussion and close communication between PMDA/MHLW and Industry regarding M&S and MIDD, such as MIDD pilot by FDA
- Build and publish a disease model etc. by promoting cross-product evaluation based on electronic data, which became mandatory to submit last year
- Promote provision of M&S information to medical sites: there have been some cases that conclusions from simulation data (popPK and/or PBPK analysis) cannot be described on Package Insert for the reason that these are not based on observed data

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  Model Informed Precision Dosing (MIPD)

Model Informed Precision Dosing (MIPD)

●What is Model Informed Precision Dosing?

- ✓ An approach that determines the optimal dose to improve the therapeutic effect and safety of the drug in individual patients based on the progression and severity of the disease, intrinsic factors (age, sex, physical constitution, state of kidney and liver function, race, genetic background, etc.), and extrinsic factors (such as combination drugs, smoking, meals, etc.)

Model Informed Precision Dosing (MIPD)

- Drug labels often say “safety and effectiveness have not been established” in special populations or mute on complicated patients (i.e., patients with moderate renal impairment and multiple concomitant moderate CYP3A4 inhibitors), leaving the dosing decision to the discretion of physicians (coined “in cerebro” modeling*)
- From the commercial perspective, “one-dose fits all” or “a couple of doses fit all” have worked and have been advocated (i.e. developing drugs with less drug-drug interaction liability)
- Model-informed precision-dosing (MIPD) is increasingly important in order to transit from “one-dose” paradigm to “precision dose”

*Clin Pharmacol Ther. 2017 May; 101(5): 646-656

Industry, government, academia discussions about MIPD

- **Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future**

  Clin Pharmacol Ther. 2017 May; 101(5): 646-656

- **Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting**

  FDA workshop with Academia and Industry, August 2019

- **Clinical Pharmacometrics: Bringing Models to Patients**

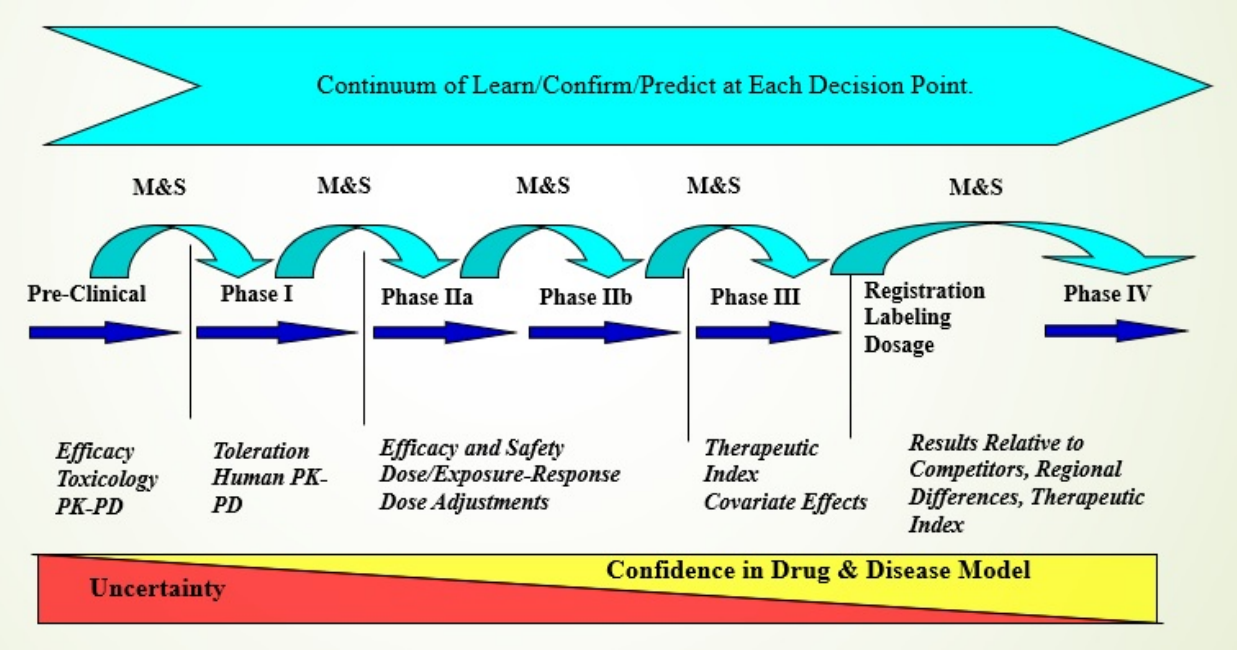
  American Conference of Pharmacometrics, October 2019

- **Further Step of Pharmacometrics: Precision Dosing**

  Annual scientific meeting of the Japanese Society of Clinical Pharmacology and Pharmaceutics, December 2020

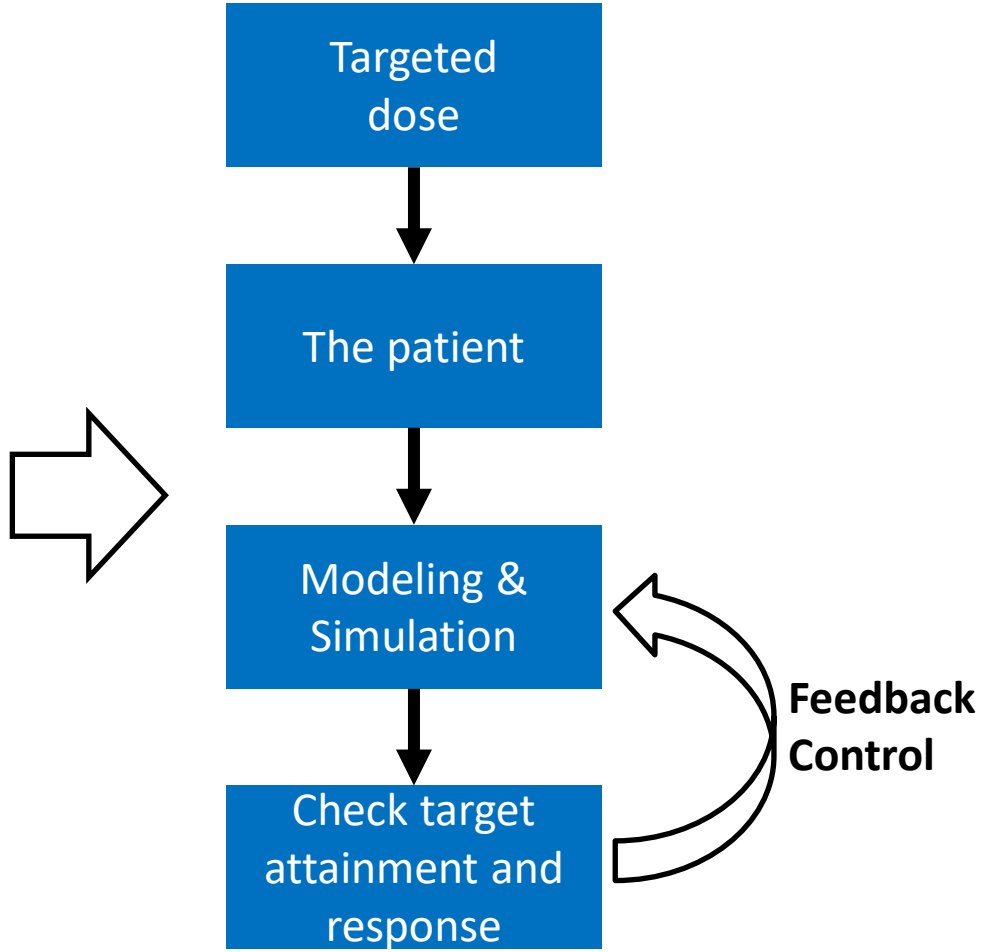
MIDD & MIPD: Future Outlook

MIDD in Clinical Development



MIPD

Implementation model-informed approach at medical practice



Clin Pharmacol Ther. 2007 Jul;82(1):21-32

Clin Pharmacol Ther. 2017 May; 101(5): 646-656

Conclusion and Take-Home Message

- We are expected to increase the number of cases which can be developed under similar clinical development strategy among Japan, EU and US to achieve worldwide simultaneous filing and approval by these three M&S guidelines and future ICH MIDD guideline.
- It is important to collaborate between regulatory authority and industry in Japan as well as globally for MIDD acceleration.
- It is also necessary to obtain sufficient understanding of MIDD from stakeholders and decision makers.
- It is required that PMDA/MHLW, Industry and Academia cooperate to share the knowledge on the model and the related information gained throughout the drug development with the medical field, in order to accelerate the appropriate usage of drug and personalized medicine.

Acknowledge

All the members of Clinical Pharmacology TF

Clinical Evaluation Expert Committee, JPMA