

Mitigation of risk and selection of clinical starting dose – a PMDA nonclinical perspective



Mineo Matsumoto DVM, PhD, DJST

Office of New Drug II

Pharmaceutical and Medical Devices Agency

Disclaimers

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency (PMDA).

Contents

1. Review Process of non-clinical safety studies in PMDA
2. Guidance for FIH Studies in Japan
3. Examples of FIH Studies in Japan
 - 1) Lesson from TGN1412
 - Estimation of FIH dose; Pharmacological approach in immunomodulators
 - 2) Lesson from BIA10-2474
4. Conclusion

Contents

1. Review Process of non-clinical safety studies in PMDA
2. Guidance for FIH Studies in Japan
3. Examples of FIH Studies in Japan
 - 1) Lesson from TGN1412
 - Estimation of FIH dose; Pharmacological approach in immunomodulators
 - 2) Lesson from BIA10-2474
4. Conclusion

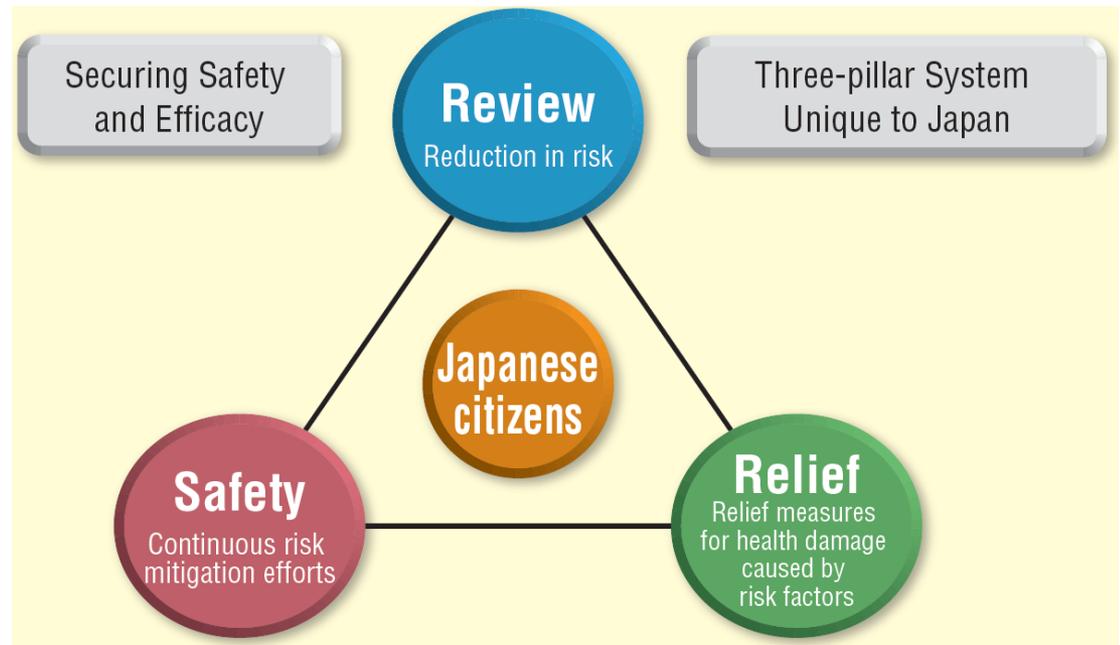
Introduction of PMDA



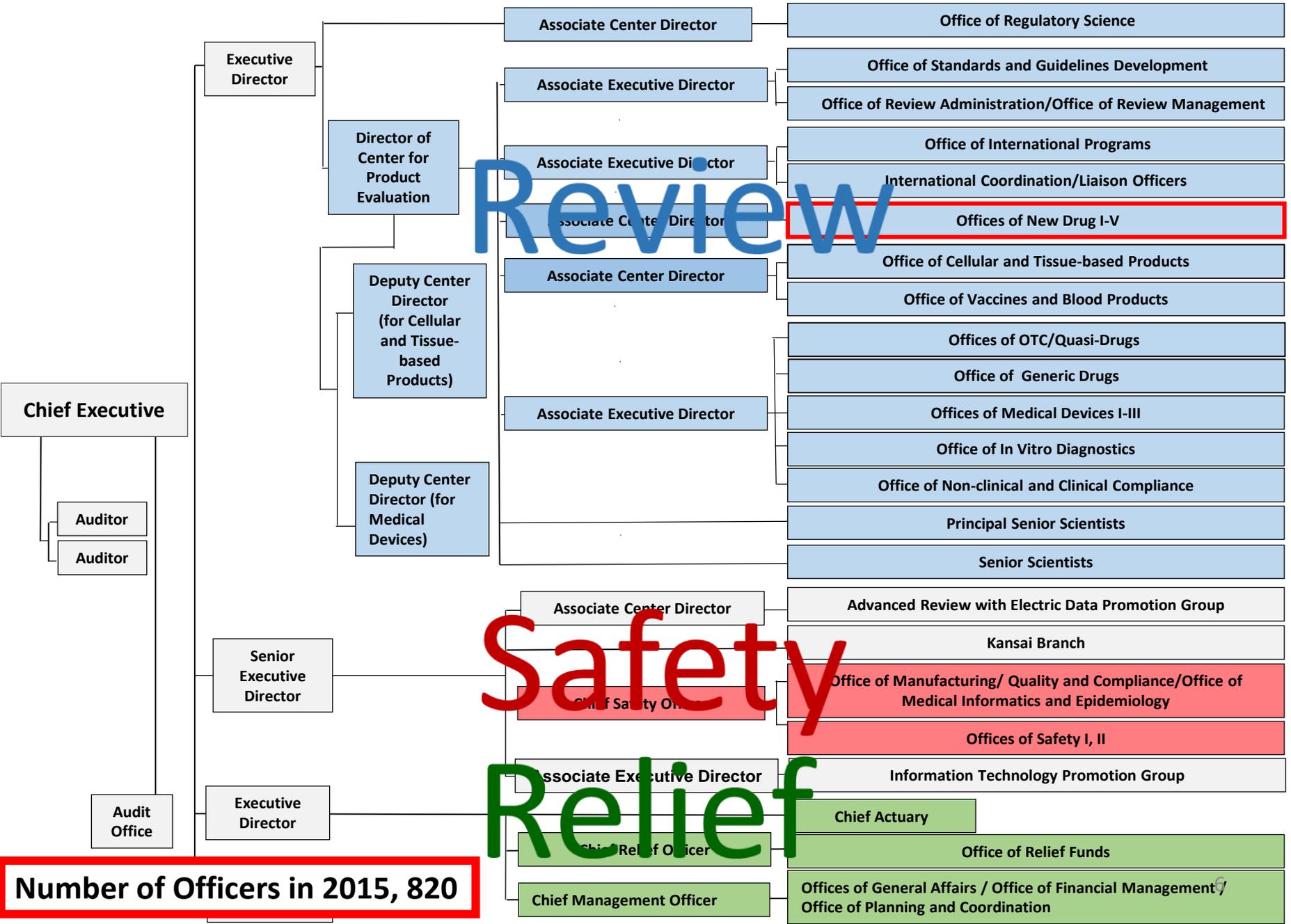
Pharmaceuticals and Medical Devices Agency (PMDA)

- ◆ an Incorporated Administrative Agency (IAA)

PMDA's Safety Triangle



Organization of PMDA



Review

Safety

Relief

Number of Officers in 2015, 820

Two Japanese Regulatory Authorities

MHLW



Ministry of Health, Labor and Welfare

Planning basic policy, enforcement of administrative measures based on the law

- Marketing authorization
- Product withdrawal
- Safety measures for emergent cases

PMDA



Pharmaceuticals and Medical Devices Agency

Review, examination and data analysis

- Scientific review and consultation
- GLP/GCP/GPSP/GMP/QMS/GCTP inspection
- Data Collection, analysis and dissemination

First Clinical trials under PMD Act

- Sponsors must not initiate the clinical trial (CT) for the period of **30 days** after submission of the first application.
- PMDA will review the CT notification in order to ensure health and hygiene and prevent any possible risks.
(**'30 day IND survey'**)

PMDA



report

MHLW

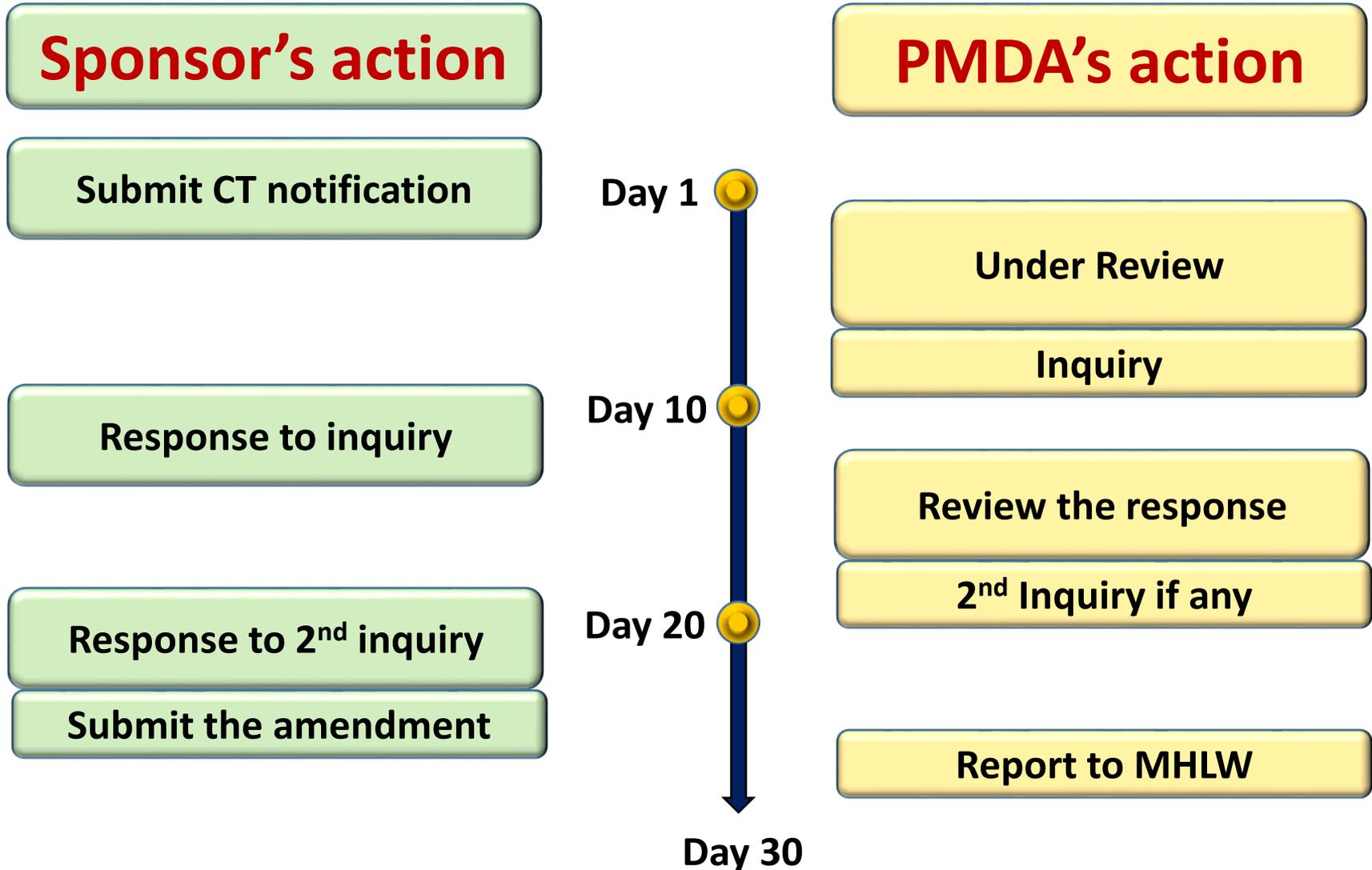


Dossier on clinical trial notification presented by sponsors

- Application form
- Rationale justifying the clinical trial
- Clinical trial protocol
- Written informed consent (IC)
- Investigator's brochure (IB)



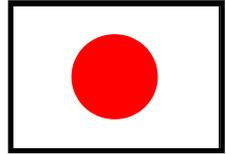
Flowchart of the '30 day IND survey'



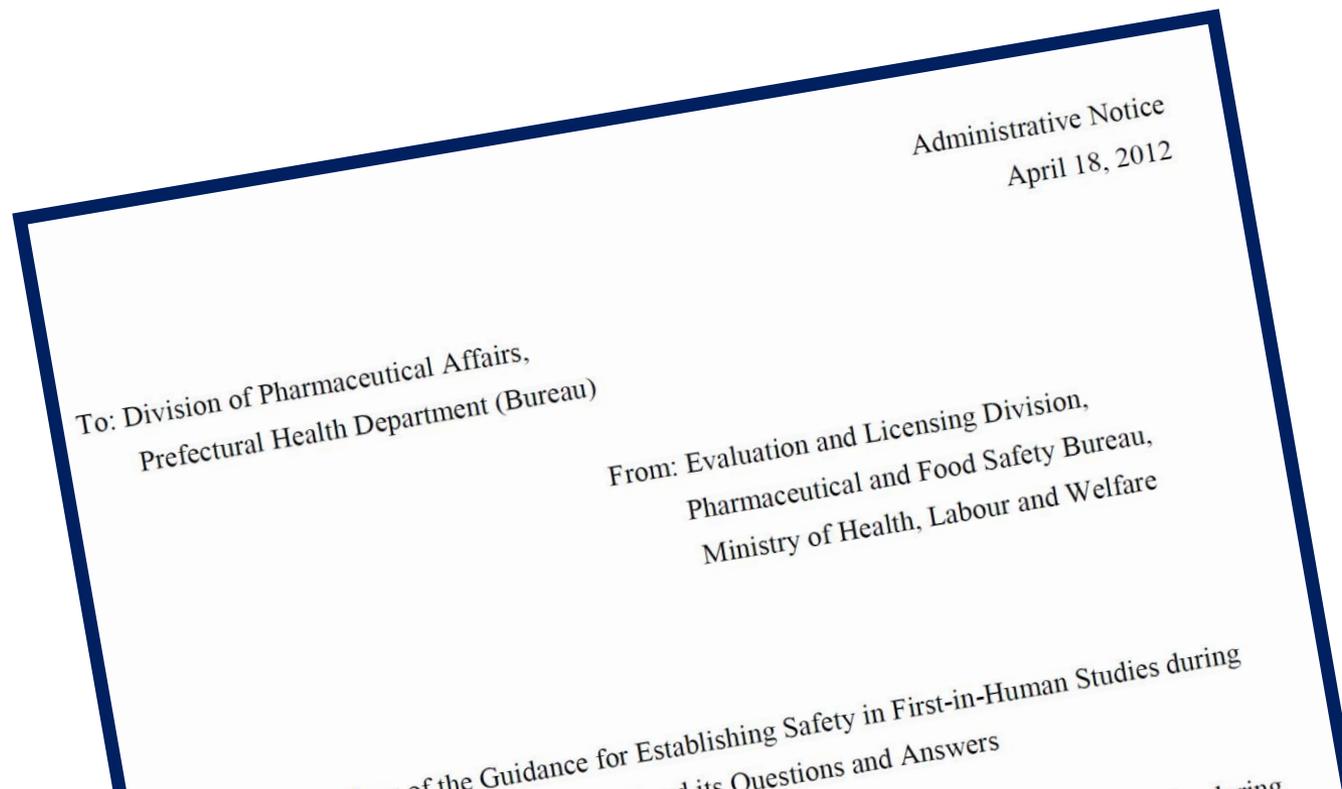
Contents

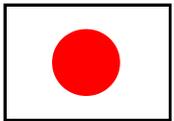
1. Review Process of non-clinical safety studies in PMDA
- 2. Guidance for FIH Studies in Japan**
3. Examples of FIH Studies in Japan
 - 1) Lesson from TGN1412
 - Estimation of FIH dose; Pharmacological approach in immunomodulators
 - 2) Lesson from BIA10-2474
4. Conclusion

Guidance for FIH Studies in Japan



‘Guidance for Establishing Safety in First-in-Human Studies during Drug Development’ (2012 Administrative notice)





Summary

1. Introduction

2. Scope

3. Main Guidance text

- Risk factors
- Investigational Product Quality
- Non-Clinical Studies

Relevance of the Animal model, Pharmacodynamics, Pharmacokinetics, Safety Pharmacology, Toxicity

- Clinical Studies

References





SUMMARY

This Guidance shows the framework of our basic concept to support the smooth transition from non-clinical to early clinical study during the drug development process. It identifies risk factors in first-in-human trials, discusses the quality of the investigational products, and describes the planning and implementation of non-clinical studies and first-in-human trials. Strategies are provided for the calculation of the initial dose to be used in humans, for subsequent dose escalation, and for the mitigation of risk to subjects that is associated with the implementation of the clinical trial.

3.4.2.b Setting the Dose for First-In-Human Administration

*Generally, the first-in-human dose will be selected as follows. First, the **No Observed Adverse Effect Level (NOAEL)** will be determined for the most highly sensitive animal species used in non-clinical studies. Next, the Human Equivalent Dose (HED) will be calculated based on those values, with the appropriate application of allometric correction or pharmacokinetic (PK) information. Considerations will include a safety factor based on the investigational product properties and the clinical study design.*

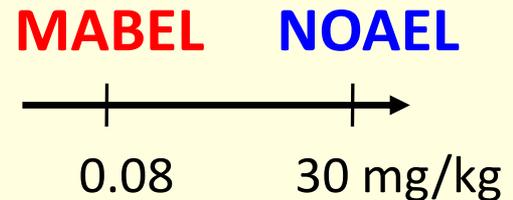
3.4 Clinical studies-3.4.1 General Principle

The trial should be designed to mitigate these risk factors, including in the following areas:

- 1. Risk related to investigational product quality*
- 2. Toxicity concerns*
- 3. Findings in appropriate animal models (non-clinical studies)*
- 4. Relevant subject population (healthy individuals, patients)*
- 5. Tolerability of anticipated adverse events/reactions in subjects*
- 6. Potential differences in reaction to the investigational product due to variability of genetic predisposition in subjects*
- 7. Possibility that patients might benefit from other available drugs and/or medical procedures*
- 8. Anticipated concentration range for the investigational product*

Contents

1. Review Process of non-clinical safety studies in PMDA
2. Guidance for FIH Studies in Japan
3. Examples of FIH Studies in Japan
 - 1) Lesson from TGN1412
 - Estimation of FIH dose; Pharmacological approach in immunomodulators
 - 2) Lesson from BIA10-2474
4. Conclusion



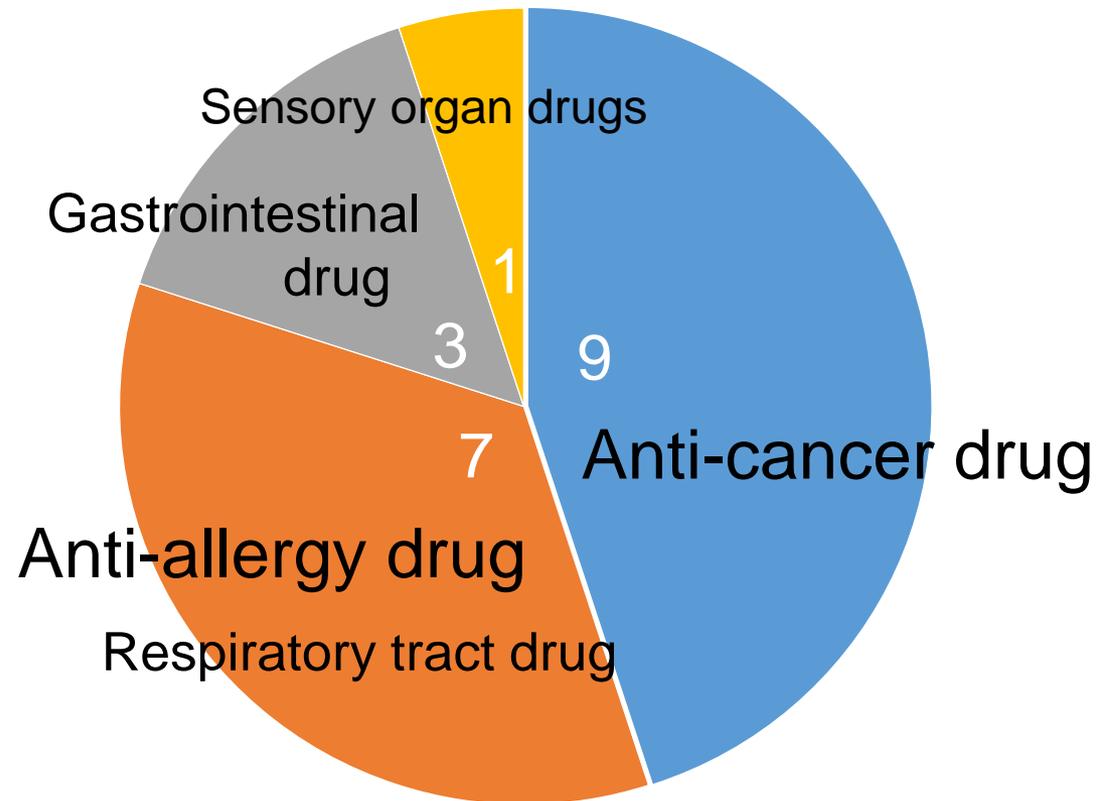
141 (25.8%)

Apr 2013~Jul 2017 (4yrs~)



20 **Immunomodulators** (excl. vaccines)

Where are they in PMDA's review teams?



Methods of estimation of FIH dose

MABEL

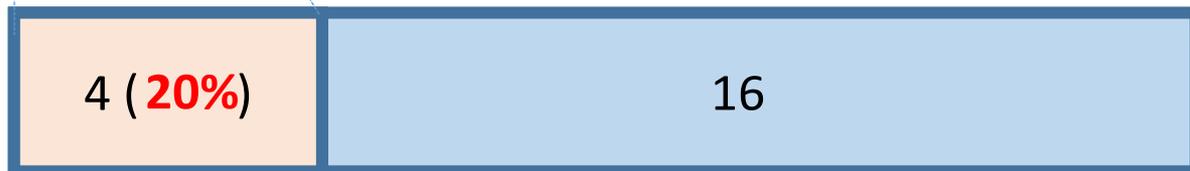
~ **PAD**

others (incl. NOAEL)

non-
Immunomodulators
121



Immunomodulators
20





3.4.2.b Setting the Dose for First-In-Human Administration

*If the **minimal anticipated biological effect level (MABEL)** is used to determine the FIH dose, investigations should be made, e.g.,*

- (1) Studies of receptor/target binding affinity and occupancy, using target human cells or cells from appropriate animal species*
- (2) Dose-response curves in target human cells or cells from appropriate animal species*
- (3) Estimated exposure in humans at pharmacological doses in appropriate animal species.*

A safety margin may be applied in the calculation of the FIH dose from the MABEL. This should take into account the novelty, bioactivity, and mode of action of the investigational product, the degree of species specificity, the shape of the dose-response curve.



3.1 Risk factors

The followings are cases where **minimal anticipated biological effect level (MABEL)** should be exercised:

- (1) No information is available on existing drugs that act on the identified target molecule,
- (2) The target molecule activates/blocks multiple signal pathways (for example, the target molecule elicits pleiotropic biological activities),
- (3) The drug elicits systemic actions in living organism such as an immune response, or
- (4) Pharmacological action may be elicited that exceeds the organism's maximum permissible limit (for example, cytokine release induced by anti-CD3- or anti-CD28-superagonist).

Drug A ~ Immunomodulator for allergy

Monoclonal antibody
Inhibition of IL-X receptor (First in class)
SC



Phase I; male, healthy volunteer, single dose, 7 days observation

Tox data

cyno monkey 3 months repeat dose tox

→ **NOAEL 30mg/kg** (no particular observation up to top dose)

Pharm data

cyno monkey disease model

700 ng/mL ; lowest concentration that exhibited the efficacy

(+ estimation based on cyno plasma concentration prediction model)

→ **MABEL 0.08 mg/kg**

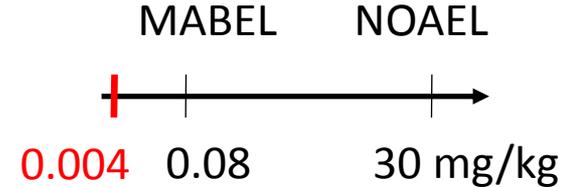
RO (receptor occupancy) at MABEL dose \doteq 90%

Drug A ~ Immunomodulator for allergy (continued)

FIH dose

0.004 mg/kg ($< 0.008 \text{ mg/kg} = 0.1 \times 0.08 \text{ mg/kg}$)

MABEL



Q1. Is NOAEL (30 mg/kg) applicable for the determination of FIH dose?

A1. No, because Drug A is an immunomodulator whose mechanism of action is novel.

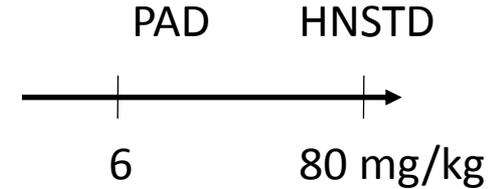
Q2. Is MABEL (0.08 mg/kg) by itself acceptable for FIH dose?

A2. No. Safety margin (~10) should be imposed on MABEL with consideration of species difference, especially because...

- 1) In vitro data is insufficient. In general, estimated value from in vivo data tends to be larger than that from in vitro data.
- 2) RO at MABEL is high (90%).

Drug B~Immunomodulator for cancer

Humanized antibody
Inhibition of CD-Y w/ potent ADCC activity
(First in class)



IV

Phase I; Cancer patients, Q2W dose, 28 days

Tox data

cyno monkey 1 month repeat dose tox
→ HNSTD 80mg/kg

Pharm data

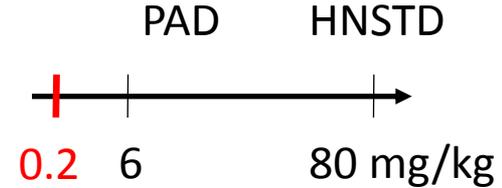
tumor xenograft mice PK/PD study
0.5 mg/kg; minimum effective dose
(+ estimation based on cyno monkey single dose study)
→ human PAD > 6 mg/kg

RO (receptor occupancy) at PAD dose \doteq 95%

Drug B ~ Immunomodulator for cancer (continued)

FIH dose

0.2 mg/kg (= $1/30 \times 6 \text{ mg/kg}$)
~PAD



Expected to have some efficacy based on Cyno single dose !

Q. Is 1/6 of HNSTD acceptable for FIH dose?

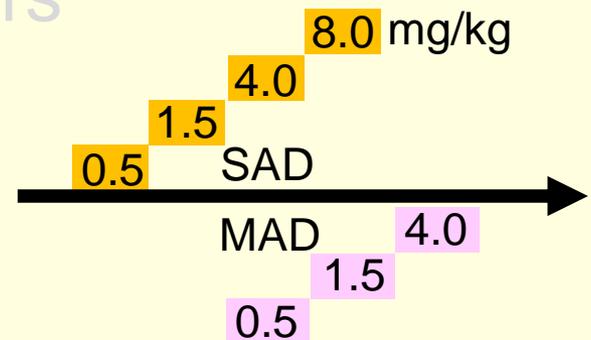
A. No, because the information is NOT sufficient with Cyno monkeys as to ..

i) whether the effect of ADCC activity can be adequately evaluated,

ii) whether CD-Y is expressed in 'organ X' that predominantly expresses CD-Y in humans.

Contents

1. Review Process of non-clinical safety studies in PMDA
2. Guidance for FIH Studies in Japan
3. Examples of FIH Studies in Japan
 - 1) Lesson from TGN1412
 - Estimation of FIH dose; Pharmacological approach in immunomodulators
 - 2) Lesson from BIA10-2474
4. Conclusion



Discussions at the Symposium over 'BIA10-2474' in Japanese Society of Toxicology meeting (Jul 2017)

1. Design of the clinical trial

· The overlap portion of SAD and MAD

The presence of the partial overlap portion itself is NOT judged to be the main cause of the incidence .

· The necessity of halting the clinical trial

In the case of BIA-2474, the side effects were expanded in the subsequent subjects in the MAD cohort 50mg without halting the trial at the timing when some effects were seen in a subject in this cohort. Thus, the trial should have been halted at that timing (opinion A) .

No, it might not have been realistic to halt the trial considering that the symptom in that particular subject was not very observable within the first 24 hrs (opinion B) .

Discussions at the Symposium over 'BIA10-2474'

in Japanese Society of Toxicology meeting (Jul 2017)

1. Design of the clinical trial (continued)

• **The required clinical PK data**

The administration at the final cohort (50mg) in MAD did not start after obtaining the PK data in the previous cohort (20mg), with only obtaining that in the previous-previous cohort (10mg). This was problematic, considering that there is a possibility of nonlinear relationship between dose and PK around those levels
(opinion A).

No, it was not a particular problem (opinion B).

• **The highest dose in MAD**

The highest dose (50mg) might have been unnecessarily too high given that the nonclinical pharmacology data had suggested the saturation of efficacy until the previous dose level.

Discussions at the Symposium over 'BIA10-2474'

in Japanese Society of Toxicology meeting (Jul 2017)

2. Handling Tox data

It is likely that mortality due to CNS symptoms in some animal species (rats, dogs, monkeys), especially the five deaths of monkeys, had not been handled properly. They all had been neglected as spontaneous cases without investigating the causal relationship with drug administration. It is noticeable that the ratio of mortality dose in monkeys with the highest human dose (50mg) was quite low (~ 8.5)

(opinion A).

The overall difficulty in histopathological examination of CNS tissue, e.g. the necessity of the optimal fixation procedure, might have been a cause of the negligence (opinion B).

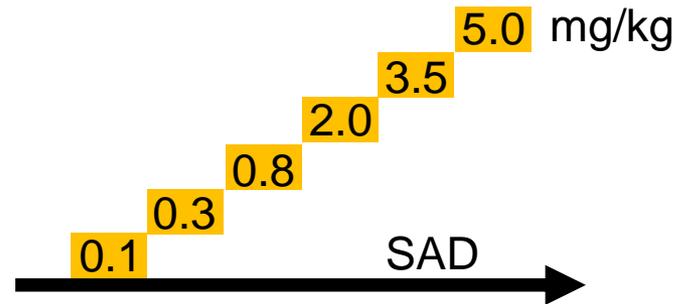
Drug C ~ New chemical entity for X disease

Small molecule

Inhibition of receptor on epithelial cells
(C_{max} dependent-action)

IV

Phase I; SAD (male, healthy volunteer)



Tox data

rat 2 wk repeat dose tox

→ NOAEL 60mg/kg (toxicity = CNS symptom at C_{max} 4000ng/mL)

dog 2 wk repeat dose tox

→ NOAEL 100mg/kg (toxicity = CNS symptom at C_{max} 5000ng/mL)

Minimum effective dose is <0.1mg/kg based on nonclinical data.

NOAEL approach was adopted for determination of FIH dose (0.1 mg/kg).

Drug C ~ New chemical entity for X disease

(continued)

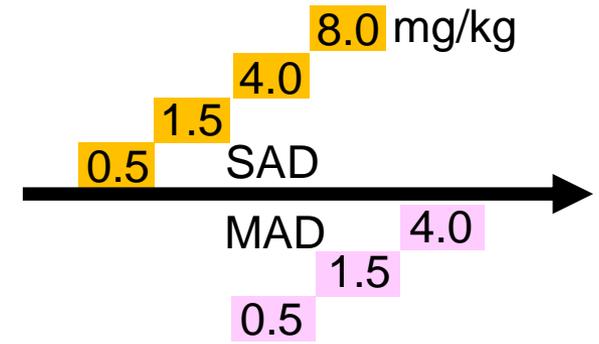
Q. Based on the tox data, cut-off value (C_{max} 4000ng/mL) is introduced as to the judge of 'Go or No-go' to the next cohort. Does the judgement that 'whether the 'average' value of C_{max} in the previous cohort actually exceeds this cut-off value' sufficiently meet this criteria?

A. No, this is not sufficient.

- Reasons)
1. The average value cannot cover potential variation. 'Variation' or 'outlier of the C_{max} value should also be taken into account for the judgement.
 2. There could be a potential nonlinearity of dose-exposure relationship. Therefore, the anticipative judgement in light of, e.g., nonclinical ADME should also be introduced even when the previous cohort does not exceed this cut-off value.
 3. Even after GO judgement is made based on the above criteria, the C_{max} value of at least the very first subject in the next cohort should be confirmed.

Drug D ~ Immunomodulator for Y disease

Monoclonal antibody
Inhibition of IL-Y (trap)
SC



Phase I; SAD (male, healthy volunteer),
MAD (male & female, patients), Q3W, 3 mo

ADME

T_{max}; 4 days, T_{1/2} 14 days (cyno monkey PK)

Tox data

cyno monkey 3 mo repeat dose tox

→ NOAEL 150mg/kg Q2W (no particular observation up to top dose)

Estimated effective dose is >3.0mg/kg based on nonclinical data.

NOAEL approach is acceptable for determination of FIH dose (0.5 mg/kg) given the presence of drugs with similar MOA and no CRS risk suggested.

Drug D ~ Immunomodulator for Y disease

(continued)

Q1. The observation period required for cohort shift in SAD is uniformly defined as Day 6 which would be longer than T_{max} of nonclinical (cyno) PK data. Is this protocol acceptable?

A1. No, the required observation period in clinical trial should be defined based on 'measured' PK data in clinical trial (e.g., the very first subject in the first cohort).

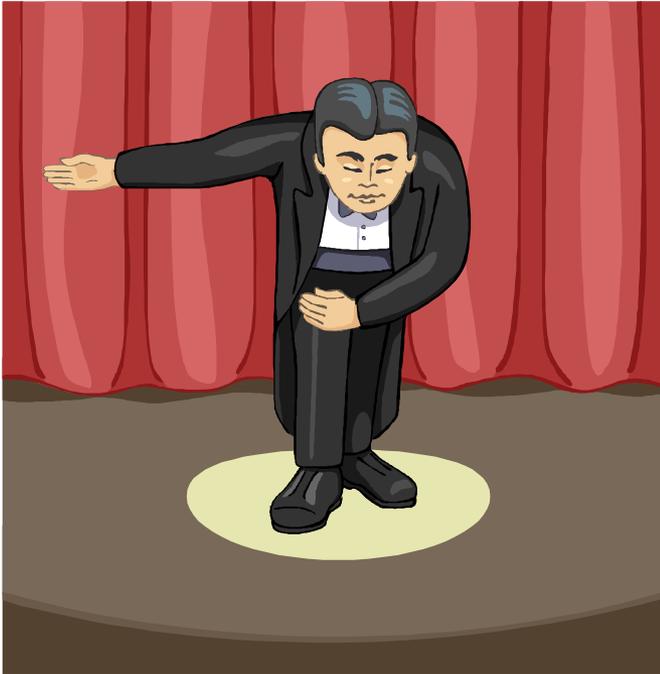
Q2. The 'Go or No-go' judgement of MAD would be solely based on the clinical observation in 1.5 mg/kg cohort in SAD. Is this protocol acceptable?

A2. No, the judgment based on clinical ADME should also be introduced, e.g., 'MAD part can start when it is anticipated that steady-state AUC_T of repeat dose will NOT exceed $AUC_{0-\infty}$ in SAD that was confirmed to show tolerability'.

Conclusion

- PMDA reviews the clinical trial notification (incl. that of FIH) within 30 days, in order to ensure safety (**‘30 day IND survey’**)
- ***Guidance for FIH Studies in Japan*** (established in 2012) is referred to for the conduct of FIH studies.
- Based on the lessons of both TGN1412 and BIA10-2474, there have been some modifications of our regulation on FIH studies.

Acknowledgement



(PMDA members)

Mizuho Nonaka

Takuya Nishimura

Keiji Hirabayashi

Misaki Naota

Mahiro Egashira

Maki Kazushige

Daisuke Maeda

Kazutoshi Shinoda

Ryuta Nakamura



<http://www.pmda.go.jp/>