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

PMDA's perspective on the evaluation of novel biomarkers

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Reviewer
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Pharmaceuticals and Medical Devices Agency

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

Outline

- Introduction
- PGx based medicine approved in Japan
- PMDA's activity related to PGx/BM
- Emerging topics

Disclaimer
The views and opinions expressed in the presentation are those of the presenter and do not necessarily reflect the official views of PMDA

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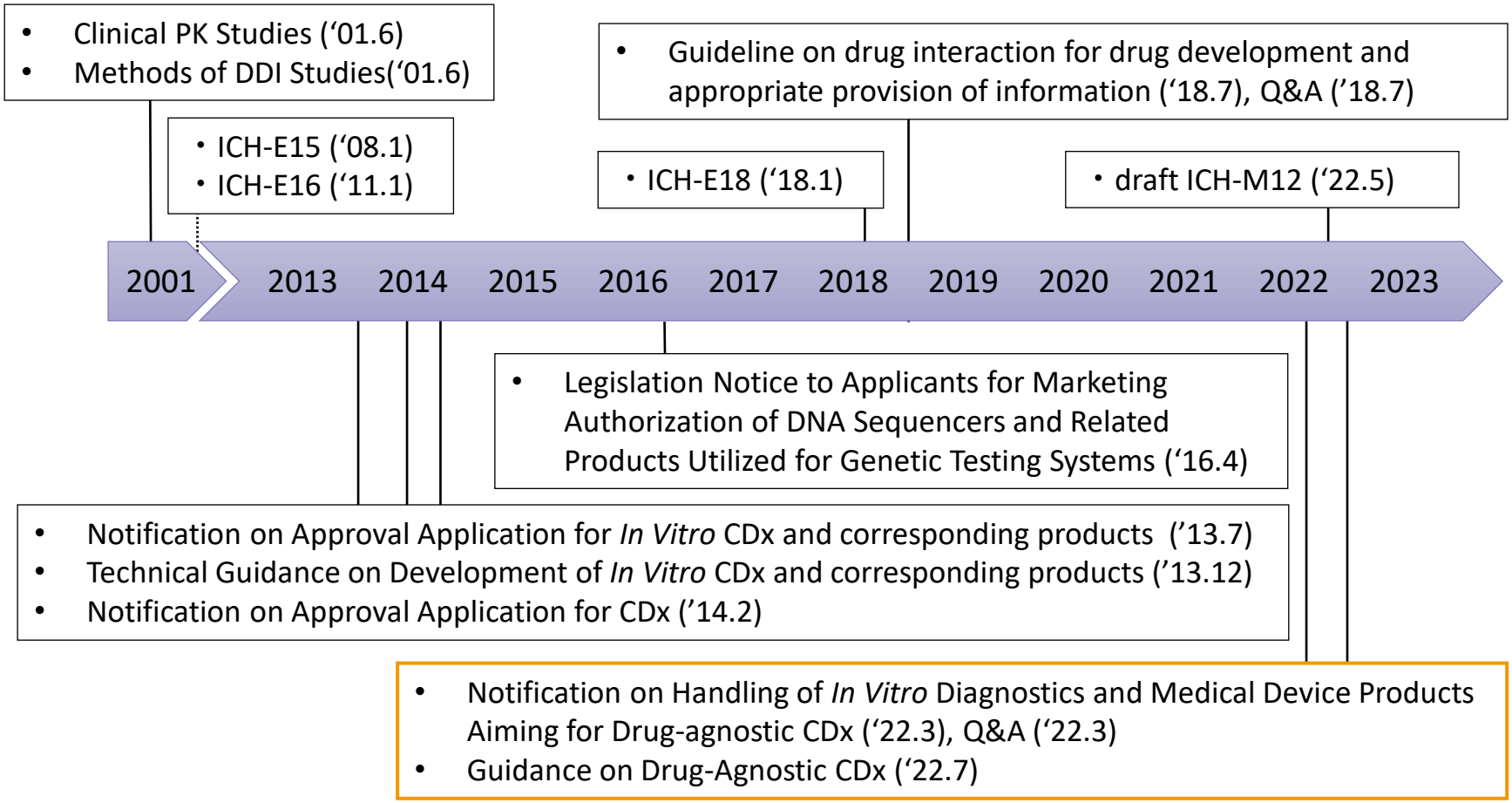
Notifications and reports related to PGx/BM issued by MHLW



BM: Biomarker, CDx: Companion Diagnostics, DDI: Drug-Drug Interaction, ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, PGx: Pharmacogenomics, PK: Pharmacokinetics

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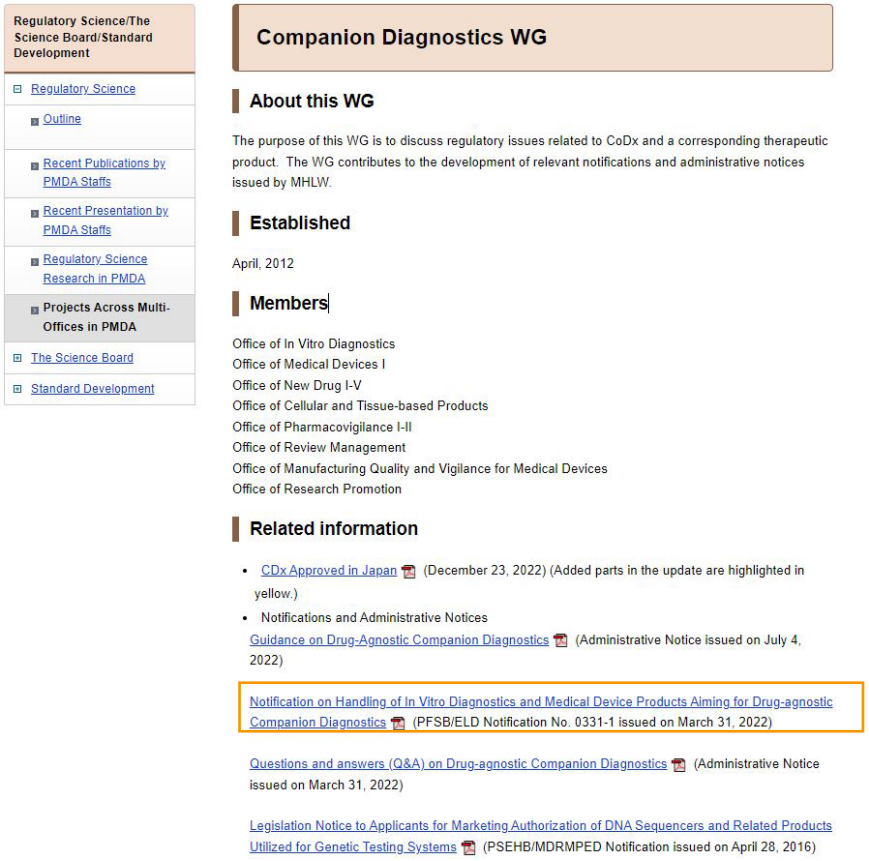

Regulatory Science/The Science Board/Standard Development

- Regulatory Science
  - Outline
  - Recent Publications by PMDA Staffs
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  - Regulatory Science Research in PMDA
  - Projects Across Multi-Offices in PMDA
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Companion Diagnostics WG

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Established

April, 2012

Members

Office of In Vitro Diagnostics
Office of Medical Devices I
Office of New Drug I-V
Office of Cellular and Tissue-based Products
Office of Pharmacovigilance I-II
Office of Review Management
Office of Manufacturing Quality and Vigilance for Medical Devices
Office of Research Promotion

Related information

- CDx Approved in Japan (December 23, 2022) (Added parts in the update are highlighted in yellow.)
- Notifications and Administrative Notices

Guidance on Drug-Agnostic Companion Diagnostics (Administrative Notice issued on July 4, 2022)

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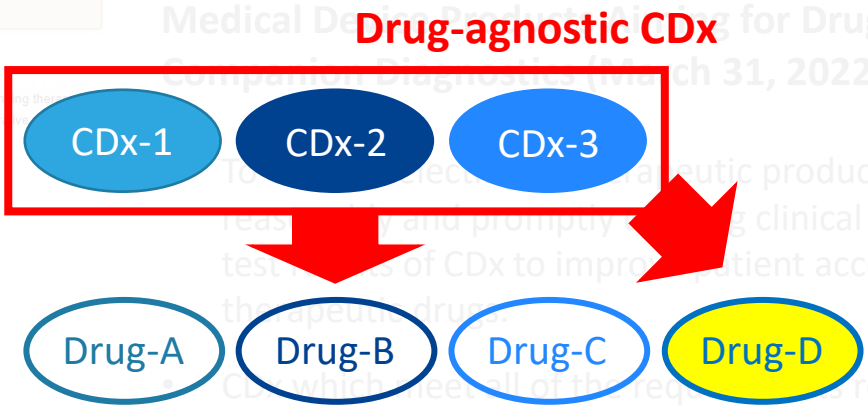
Notification on Handling of *In Vitro* Diagnostics and Medical Device Products Aiming for Drug-agnostic Companion Diagnostics (March 31, 2022)

- To enable selecting of therapeutic products reasonably and promptly utilizing clinical laboratory test results of CDx to improve patient access to therapeutic drugs.
- CDx which meet all of the requirements referred to as "drug-agnostic CDx“
- If it can be adequately explained that the approved drug-agnostic CDx can be used to identify the eligible patients for treatment with the target therapy of a new therapeutic product, ..., an application for partial change approval of drug-agnostic CDx is not required in association with the submission of the application of the new therapeutic product.

Notifications and reports related to PGx/BM issued by MHLW



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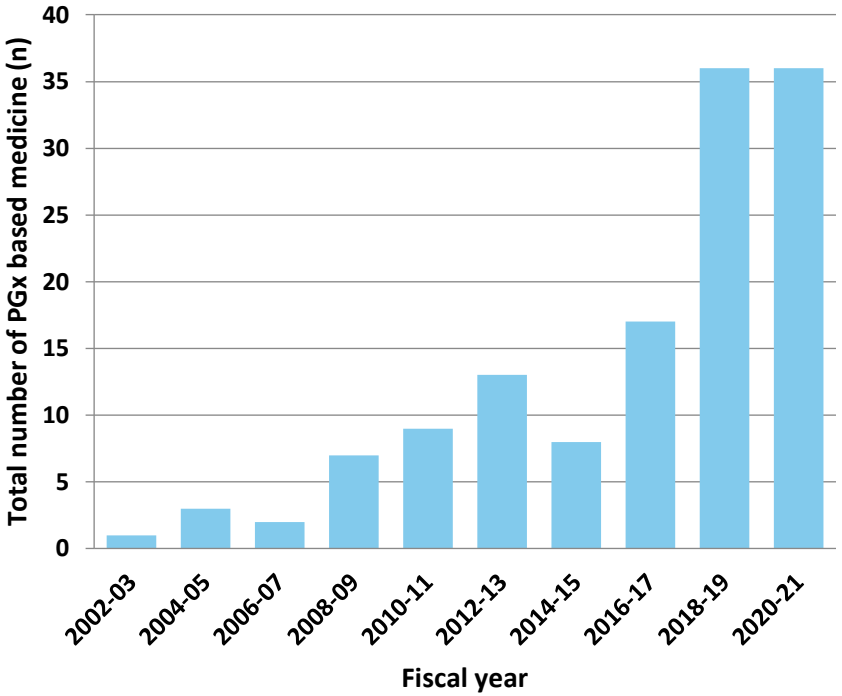
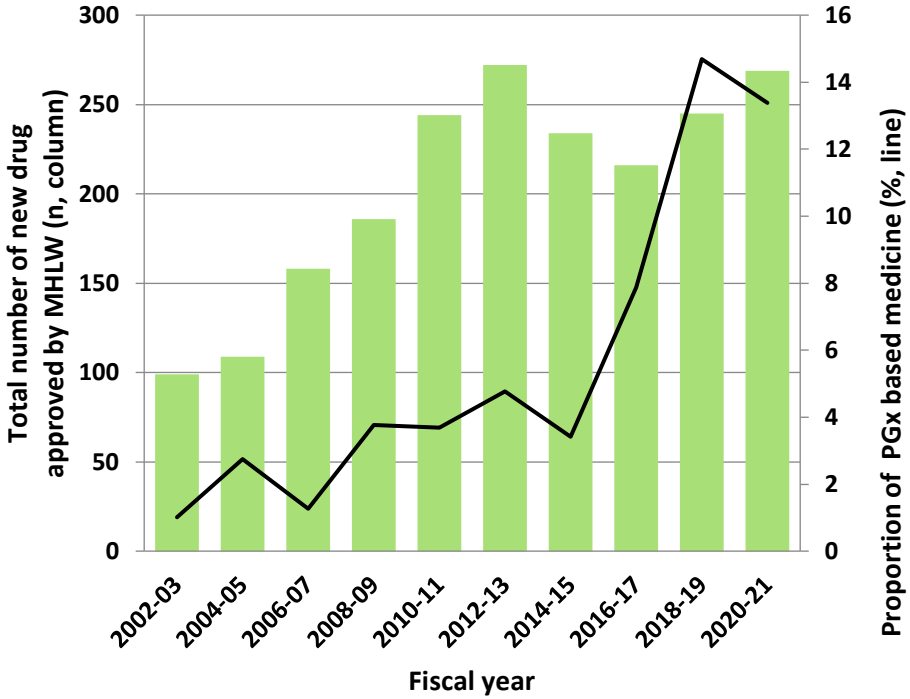
Approval drugs with PGx information listed on their labels in Japan

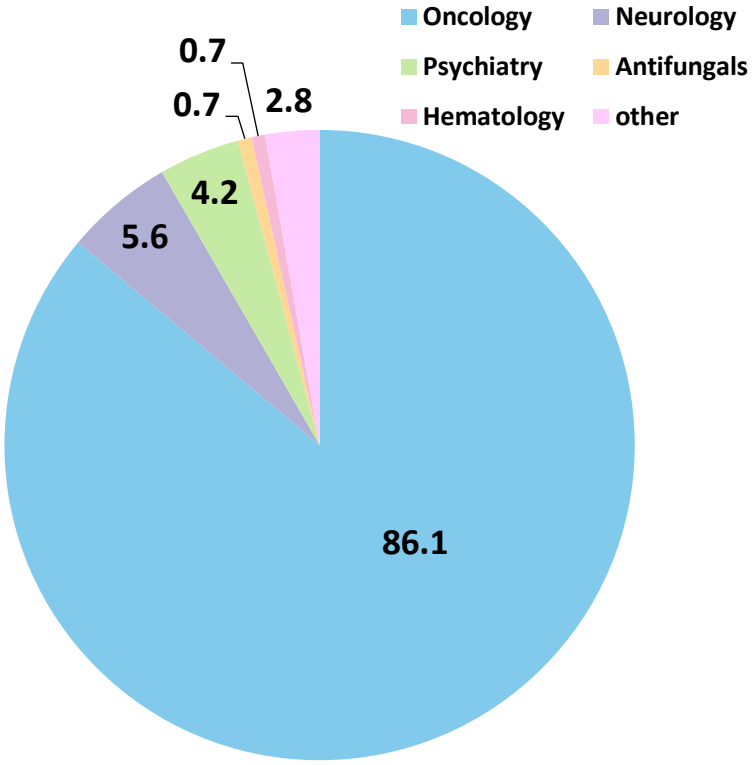
- PGx based medicine approved from FY2002 to 2021

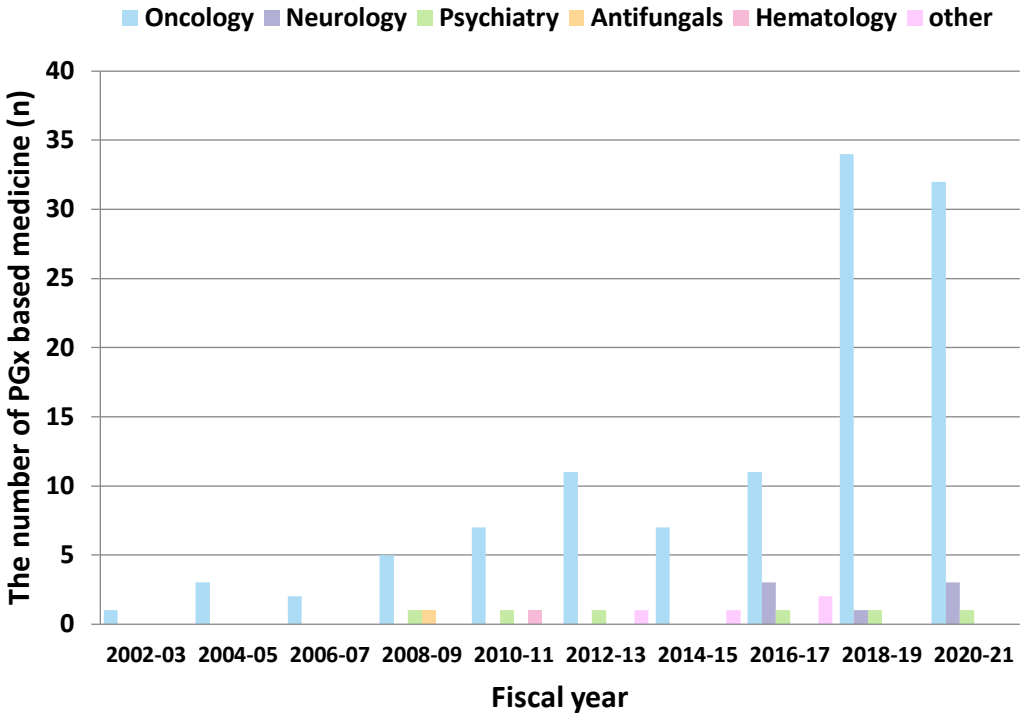




Approval drugs with PGx information listed on their labels in Japan

- Targeted disease area of PGx based medicine approved from FY2002 to 2021





Approval drugs with PGx information listed on their labels in Japan

- Example of PGx information on drug labels; Larotrectinib and NTRK fusion gene

Larotrectinib Label (’21.3)

[Indication]

*NTRK*融合遺伝子陽性の進行・再発の固形癌

[Precautions for indication]

5.1 十分な経験を有する病理医又は検査施設における検査により、*NTRK*融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

- Drug with a new active ingredient indicated for the treatment of NTRK fusion gene-positive advanced or recurrent solid tumors.
- This drug is not targeting specific type of cancer.

Approval drugs with PGx information listed on their labels in Japan

- Example of PGx information on drug labels; Siponimod and CYP2C9 alleles

Siponimod Label (’20.6)

[Contraindication]

2.9 CYP2C9*3/*3を保有している患者［7.3 参照］

[Precautions for dosage and administration]

7.3 本剤投与開始前にCYP2C9遺伝子型を確認すること。［2.9、7.4、9.1.1、15.1.1、16.6.3 参照］

7.4 CYP2C9*1/*3又は*2/*3を保有する患者については、維持用量は1日1回1mgとすることが望ましい。維持用量を1日1回1mgとする場合は、4日目までは用法及び用量と同様に漸増を行い、5日目以降は1mgとすること。［7.3、9.1.1、15.1.1、16.6.3 参照］

16.6.3 CYP2C9遺伝子型

CYP2C9の遺伝子型*1/*1、*2/*3及び*3/*3を保有する健康成人（24例）に本剤0.25mgを単回経口投与したとき、*2/*3及び*3/*3を保有する健康成人のシポニモドのAUCは、*1/*1を保有する健康成人に比べて、それぞれ2.05倍（90%信頼区間：1.71,2.45）及び3.84倍（90%信頼区間：3.22,4.59）高かった（Cmaxはそれぞれ1.21倍［90%信頼区間：1.02,1.44］及び1.16倍［90%信頼区間：0.98,1.37］高かった）。*1/*1、*2/*3及び*3/*3を保有する健康成人におけるシポニモドの$t_{1/2}$はそれぞれ28、51及び126時間であった[13]（外国人データ）。

二次性進行型多発性硬化症患者を対象とした母集団薬物動態解析から、CYP2C9*1/*1及び*1/*2を保有する被験者のCL/Fが3.11L/hと推定されたのに対し、*2/*2、*1/*3、*2/*3を保有する被験者ではそれぞれ2.5、1.9及び1.6L/hと推定された。AUCはそれぞれ1.25、1.61、1.91倍に増加すると予測された[14,15]。

また、第Ⅰ相及び第Ⅱ相試験結果を用いた母集団薬物動態解析から、*3/*3を保有する被験者のCL/Fは0.9L/hと推定され、AUCは3.84倍に増加すると予測された[15,16]。［7.3、7.4、9.1.1、10.2、15.1.1 参照］

- Concentration of Siponimod was increased in healthy subjects having CYP2C9 alleles (*2/*3, *3/*3)
- Patients-based PPK analysis predicts that concentration of Siponimod is increased in subjects with CYP2C9 alleles (*2/*2, *1/*3, *2/*3)

＊Genotyping of CYP2C9 gene is covered by National Health Insurance in Japan

Biomarker	Intended use	Fees*	Approved Year
CYP2C9 (*2/*3)	Qualitative genotyping of drug-metabolizing enzyme CYP2C9 gene polymorphisms (*2,*3) in genomic DNA extracted from whole blood or oral mucosa	20,370 Yen	2021

Approval drugs with PGx information listed on their labels in Japan

- Example of PGx information on drug labels; Irinotecan and UGT1A1 alleles

Irinotecan Label (’08.6)

[Important Precautions]

(10) 本剤の活性代謝物(SN-38)の主な代謝酵素であるUDP-グルクロン酸転移酵素(UDP-glucuronosyltransferase、UGT)の2つの遺伝子多型(*UGT1A1*6*、*UGT1A1*28*)について、いずれかをホモ接合体(*UGT1A1*6/*6*、*UGT1A1*28/*28*)またはいずれもヘテロ接合体(*UGT1A1*6/*28*)としてもつ患者では、UGT1A1のグルクロン酸抱合能が低下し、SN-38の代謝が遅延することにより、重篤な副作用(特に好中球減少)発現の可能性が高くなることが報告されているため、十分注意すること(「薬物動態」、「臨床成績」の項参照)[1)~3)]。

[Clinical Studies]

【UGT1A1遺伝子多型と副作用発現率】[3)]

本剤単独投与(55例)の各種癌患者について、UGT1A1遺伝子多型と副作用との関連性について検討した。本剤は、100mg/m²を1週間間隔または150mg/m²を2週間間隔で投与した。

グレード3以上の好中球減少および下痢の発現率は次表のとおりであった。

遺伝子多型	グレード3以上の好中球減少発現率(例数)	グレード3の下痢発現率(例数)
*UGT1A1*6*と*UGT1A1*28*をともにもたない	14.3% (3/21)	14.3% (3/21)
*UGT1A1*6*または*UGT1A1*28*をヘテロ接合体としてもつ	24.1% (7/29)	6.9% (2/29)
*UGT1A1*6*または*UGT1A1*28*をホモ接合体としてもつ、もしくは*UGT1A1*6*と*UGT1A1*28*をヘテロ接合体としてもつ	80.0% (4/5)	20.0% (1/5)

- UGT1A1 alleles *(*6 and *28*) have been reported to be associated with a risk of irinotecan-induced SAE (neutropenia)
- Data from prospective study showed the higher frequency of neutropenia in the Japanese subjects homozygous for **6* or **28* or double heterozygous *(*6/*28*)

Approval drugs with PGx information listed on their labels in Japan

- Example of PGx information on drug labels; Irinotecan and UGT1A1 alleles

Irinotecan Label (’13.12)

[Precautions for indications]

(1) 治癒切除不能な膵癌の場合、患者の病期、全身状態、UGT1A1[注]遺伝子多型等について、「臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

注)本剤の活性代謝物(SN-38)の主な代謝酵素の一分子種である。

[Clinical Studies]

国内で実施された、化学療法未治療の遠隔転移を有する膵癌を対象とした第Ⅱ相臨床試験におけるFOLFIRINOX法(1クールを2週間として第1日目にオキサリプラチン85mg/m^2、レボホリナート200mg/m^2、本剤180mg/m^{2}を点滴静注し、引き続きフルオロウラシル400mg/m^{2}を急速静脈内投与、フルオロウラシル2,400mg/m^{2}を46時間かけて持続静注)の成績は次表のとおりであった[26]。対象患者はECOG Performance status 0及び1であった。2つの遺伝子多型(*UGT1A1*6*、*UGT1A1*28*)について、いずれかをホモ接合体(*UGT1A1*6/*6*、*UGT1A1*28/*28*)又はいずれもヘテロ接合体(*UGT1A1*6/*28*)としてもつ患者は除外された。また、1クール目の投与可能条件として、好中球数(2,000/mm^{3}以上)、総ビリルビン値(施設基準値上限以下)等が設定された。

疾患名	奏効率(有効例/適格例)
化学療法未治療の遠隔転移を有する膵癌	38.9%(14/36)

- Prospective Japanese phase II study excluding patients with UGT1A1 alleles (*6/*6 , *28/*28, *6/*28) has been conducted for new additional indication for the treatment of unresectable pancreatic cancer
- These descriptions were added at the time of approval for pancreatic cancer

Approval drugs with PGx information listed on their labels in Japan

- Example of PGx information on drug labels; Irinotecan and UGT1A1 alleles

Liposomal Irinotecan Label (’20.3)

[Precautions for dosage and administration]

7.2 *UGT1A1*6*若しくは*UGT1A1*28*のホモ接合体を有する患者、又は*UGT1A1*6*及び*UGT1A1*28*のヘテロ接合体を有する患者では、イリノテカンとして1回50mg/m^{2}を開始用量とする。なお、忍容性が認められる場合には、イリノテカンとして1回70mg/m^{2}に増量することができる。[9.1.2 参照]

[Clinical Studies]

17.1.1 国内第Ⅱ相試験

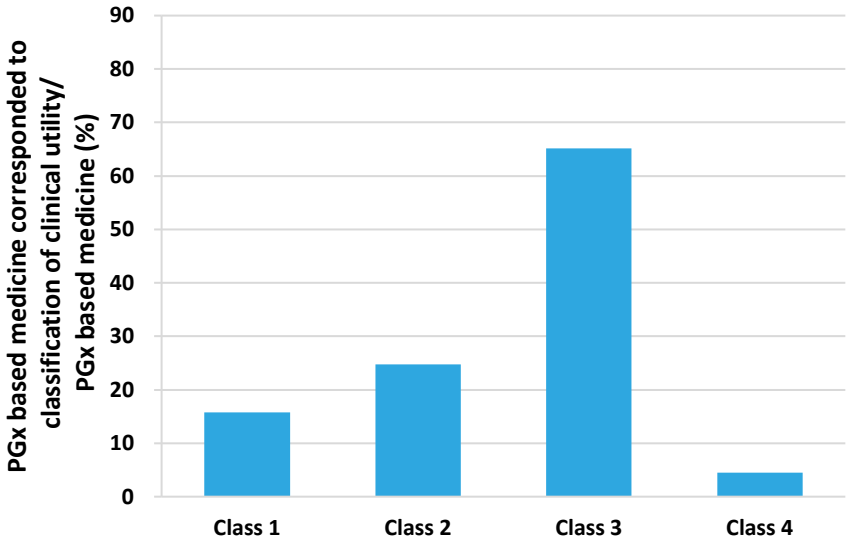
ゲムシタビンを含む化学療法後に増悪した遠隔転移を有する膵癌患者[注1)]を対象として、本剤（イリノテカンとして70mg/m^2）[注2)]とフルオロウラシル及びレボホリナートの併用投与（本剤+5-FU/*l*-LV）と5-FU/*l*-LVの有効性及び安全性を比較する第Ⅱ相臨床試験を実施した[注3)]。主要評価項目とされた独立中央判定委員会の評価による無増悪生存期間（PFS）の結果（2017年5月4日データカットオフ）は表3及び図2のとおりであった。

注2）*UGT1A1*6*若しくは*UGT1A1*28*のホモ接合体を有する患者、又は*UGT1A1*6*及び*UGT1A1*28*のヘテロ接合体を有する患者ではイリノテカンとして50mg/m^{2}で開始された。

- Prospective Japanese phase II study has been conducted for new indication in a new dosage for the treatment of unresectable pancreatic cancer that has progressed after cancer chemotherapy
- In this study, liposomal irinotecan was started to dose at 50 mg/m^2 for patients with UGT1A1 alleles (*6/*6 , *28/*28, *6/*28)

Approval drugs with PGx information listed on their labels in Japan

- PGx based medicine approved from FY2016 to 2021 corresponds to classification of clinical utility



	Classification	Example cases
1	**Clinically useful drug with new mechanism of action**	• Drugs with new active mechanism, which have efficacy in non-responder to conventional therapies • Drugs with new active mechanism, which provide treatment options for serious/intractable diseases for which there is no or extremely limited existing treatment. ✓ Applications for additional indications or dosage/administration are excluded from this class
2	**Drug with higher efficacy profile justified statistically**	• In terms of efficacy, the superiority has been confirmed against conventional therapies ✓ Count as class 3 if the drug has demonstrated superiority over existing therapies, but the position of the drug is unknown because it has not been compared with similar drugs that are in development ahead of it.
3	**Drug with clinically useful efficacy other than 1-2**	• Drug which have efficacy in non-responder to conventional therapies • Recommended level in pertinent guidelines is higher than existing drug • Novel therapeutic option for diseases without existing treatment
4	**Drug with clinical utility other than efficacy (e.g., convenience)**	• Frequency of administration decreases dramatically • New route of administration (eg, Establishment oral treatment for disease that there is only intravenous administration treatment)

CDx products approved in Japan

Regulatory Science/The Science Board/Standard Development

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List of *in vitro* Companion Diagnostics or Medical Devices (CDx Products) Approved in Japan

	Therapeutic products used with CDx products			CDx products	
No.	Proprietary name	Active substance name	Indications	*In vitro* companion diagnostics or medical devices*	Biomarkers
1	ERBITUX Injection 100mg	Cetuximab (genetical recombination)	Colorectal cancer	MEBGEN RASKET-B kit	*KRAS/NRAS* mutation
				OncoBEAM RAS CRC Kit	
				FoundationOne CDx	
2	ALUNBRIG Tablets 30mg, 90mg	Brigatinib	Non-small cell lung cancer	Vysis ALK Break Apart FISH probe kit	*ALK* fusion
				AmoyDx Pan Lung Cancer PCR Panel	
				Oncomine Dx Target Test	
				FoundationOne CDx	
				Lung Cancer Compact Panel Dx Multiplex Companion Diagnostic System	
				Ventana OptiView ALK (D5F3)	ALK protein
				Histofine ALK iAEP kit	
3	ALECENSA Capsules 150mg	Alectinib Hydrochloride	Non-small cell lung cancer	Histofine ALK iAEP kit**	CCR4 protein
				Ventana OptiView ALK (D5F3)	
				Vysis ALK Break Apart FISH probe kit**	*ALK* fusion
				Oncomine Dx Target Test	
				FoundationOne CDx	
				FoundationOne Liquid CDx	
				AmoyDx Pan Lung Cancer PCR Panel	
				Lung Cancer Compact Panel Dx Multiplex Companion Diagnostic System	
4	IRESSA Tablets 250	Gefitinib	Non-small cell lung cancer	Cobas EGFR mutation test v2.0	*EGFR* mutation
				Oncomine Dx Target Test	
				therascreen EGFR RGQ PCR kit	
				FoundationOne CDx	
				EGFR LIQUID	
				FoundationOne Liquid CDx	
				AmoyDx Pan Lung Cancer PCR Panel	
				Lung Cancer Compact Panel Dx Multiplex Companion Diagnostic System	
5	VITRAKVI capsules 25mg, 100mg VITRAKVI oral solution 20mg/mL	Larotrectinib Sulfate	Solid cancer	FoundationOne CDx	NTRK1/2/3 fusion
6	VANFLYTA TABLETS 17.7mg, 26.5mg	Quizartinib Hydrochloride	Acute myeloid leukemia	LeukoStrat CDx FLT3 Mutation Assay	*FLT3* mutation
7	OPDIVO I.V.Infusion 20mg, 100mg, 120mg, 240mg	Nivolumab (genetical recombination)	Colorectal cancer	MSI kit (FALCO)	MSI-High
				FoundationOne CDx	
				Guardant360 CDx	
				Idylla MSI Test (NichireiBio)	
			Non-small cell lung cancer Esophageal cancer Breast cancer	PD-L1 IHC 22C3 pharmDx [Dako]	PD-L1 protein
				MSI kit (FALCO)	MSI-High
				FoundationOne Liquid CDx	
				Guardant360 CDx	

List of *in vitro* Companion Diagnostics or Medical Devices (CDx Products) Approved in Japan is available on PMDA website

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- Emerging topics

PMDA's activities to encourage PGx/BM utilization

Omics working group

- Representatives of Offices of New Drugs, Medical Devices, Conformity Audit, Safety in PMDA

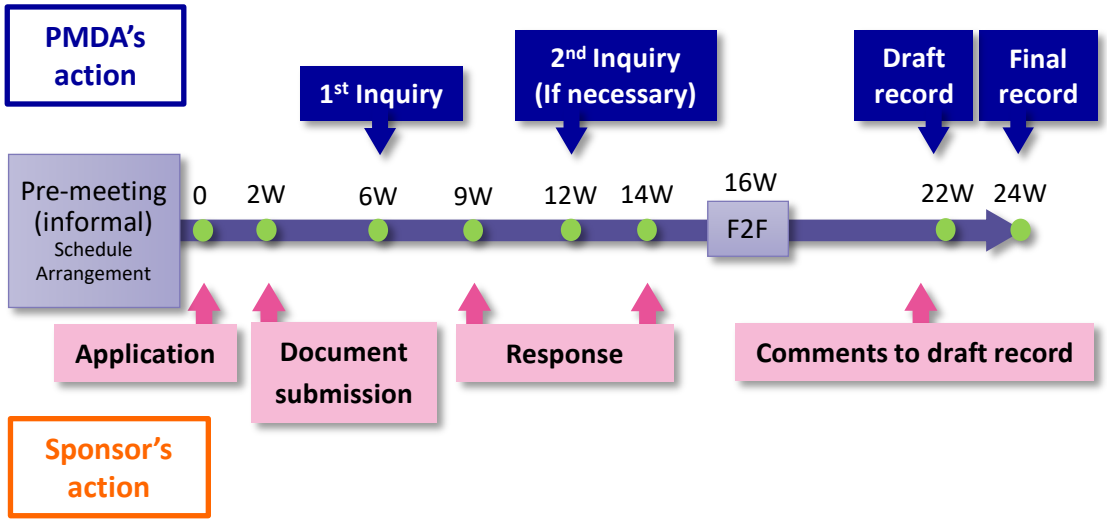
- Review BM qualification submissions which are NOT related to individual drugs/devices
  - ✓ PMDA's formal scientific consultation regarding BM qualification
  - ✓ Informal meetings with industry, academic scientists

- Discuss regulatory issues relating to Omics, i.e., PGx

PMDA's activities to encourage PGx/BM utilization

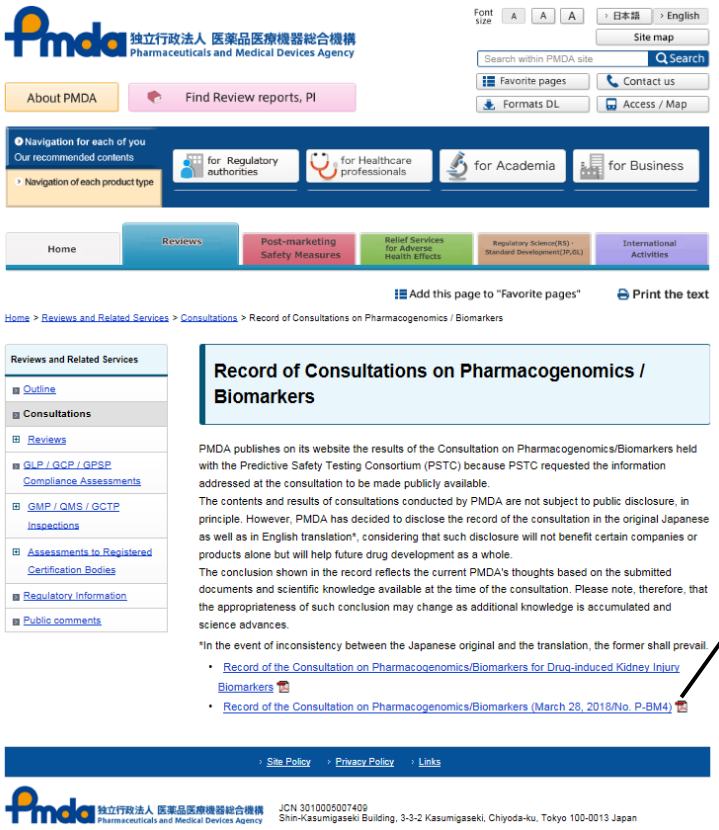
Consultation on PGx/BM

Timeline of Consultation on PGx/BM



PMDA's activities to encourage PGx/BM utilization

Consultation on PGx/BM



This English version of the record of the consultation has been published by PMDA. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

(Attachment 1)

Record of the Consultation on Pharmacogenomics/Biomarkers

November 2, 2018
Pharmaceuticals and Medical Devices Agency

Concerning the following consultation on Pharmacogenomics/Biomarkers requested, the background of the consultation submitted by applicant (hereinafter referred to as the "applicant") and the summary of an evaluation by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "PMDA") are as described herein.

It should be noted that decisions in this document were made on the scientific level at the time of face-to-face consultation based on the data submitted by the applicant. Interpretation for the validity of the decisions may vary based on possible new findings and scientific advances, etc.

Date/No. of reception:	March 28, 2018/No. P-BM4
Biomarkers consulted:	Urinary clusterin, urinary cystatin C, urinary kidney injury molecule-1 (KIM-1), urinary *N*-Acetyl-*beta*-*D*-Glucosaminidase (NAG), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary osteopontin, urinary total protein, and urinary albumin
Consultation category:	Additional consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)
Consultation applicant:	Critical Path Institute's Predictive Safety Testing Consortium (PSTC)
Department in charge (Section):	Omics Working Group

Publication will be accepted when it is anticipated to contribute improving public health, i.e., to promote further development of novel safety BMs

PMDA's activities to encourage PGx/BM utilization

Case examples of Consultation on PGx/BM with PSTC

- At this consultation the applicant discussed the plan for qualification of 8 Novel BMs (urinary clusterin, urinary cystatin C, urinary kidney injury molecule-1, urinary *N*-Acetyl-*beta*-*D*-glucosaminidase, urinary neutrophil gelatinase-associated lipocalin, urinary osteopontin, urinary total protein, and urinary albumin) which are considered to be applicable for prediction of renal injury in medical practice based on the results of clinical studies in the Learning Phase.

- To verify the qualification of the Novel BMs in Japanese subjects, the applicant proposed the bridging strategy.

- It was planed to evaluate the ethnic differences based on the results of the 4 clinical studies conducted in non-Japanese subjects (Cisplatin Study, Aminoglycoside Study, HV Study and MM Study) compared on a step-by-step basis, first with data in Japanese healthy subjects, and then with the data in Japanese subjects with renal impairment

https://www.pmda.go.jp/review-services/f2f-pre/consultations/0008.html

PMDA's activities to encourage PGx/BM utilization

Discussions in the consultation (1)

- The PMDA, however, thinks that it is important to make the background characteristics of subjects in renal toxic drug treatment and non-renal toxic drug treatment groups in the bridging studies in Japanese subjects as similar as possible to those in the clinical studies (cisplatin study and aminoglycoside study) in the confirmatory phase so that ethnic differences in the Novel BMs for drug-induced renal disorder can be properly assessed.

- In addition, the PMDA commented as follows: As the PMDA pointed out at the Previous Consultation, changes over time in the Novel BMs (e.g., timing when the biomarkers start to elevate, the duration and recovery of the evaluation, etc.) are considered to be important information for correctly understanding the nature of the Novel BMs and measuring them in a timely manner; thus, such changes should be evaluated to the extent possible based on the results of the studies in the confirmatory phase and the bridging studies in Japanese subjects.

PMDA's activities to encourage PGx/BM utilization

Discussions in the consultation (2)

- This study should be conducted as a prospective study in order to appropriately compare the data collected with the results of the HV Study, which was also conducted as a prospective study.

- Therefore, the applicant should set out a criteria to demonstrate "similarities" or "the absence of problematic difference" compared to the results of HV Study (for instance, the confidence interval of the specificity in this study to be within X% of the confidence interval of the specificity in HV Study), in addition to visual inspection and/or other descriptive statistical assessments as a statistical analysis technique.

PMDA's activities to encourage PGx/BM utilization

Discussions in the consultation (3)

- In order to enable accurate discussions on the similarities in Novel BMs between Japanese and non-Japanese, this study should be conducted as a prospective study, and all factors except for the ethnic (regional) factors (e.g., underlying disease, the severity of renal function, types of nephrotoxic drugs, and timepoints for sample collection, etc.) should be the same, as much as possible, as those of prospective studies conducted in non-Japanese subjects.

- Comparisons based on the data such as sensitivity, specificity, and ROC (Receiver Operating Characteristic) analysis are important in evaluating the similarities of Novel BMs between Japanese and non-Japanese; thus, subjects not receiving a nephrotoxic drug should be also enrolled in the study so as to discuss these data in Japanese patients. Moreover, as shown in the PMDA's opinion in above 1), carefully consider the necessity to set out criteria that enables appropriate judgment of the similarities.

PMDA's activities to encourage PGx/BM utilization

Empiric perspectives based on PGx/BM consultations

- The context of use should be clearly stated what is possible and are the limitations of measuring the biomarker, and it is necessary to explain how the measurement of biomarkers brings clinical benefits
- Non-clinical qualification should be conducted depending on the context of use of BMs (e.g., predictive BMs for rare and severe adverse drug reactions)
- Basically, a prospective evaluation is needed to clarify the clinical significance of using the biomarker
- It is desirable to examine the ethnic differences of the biomarker

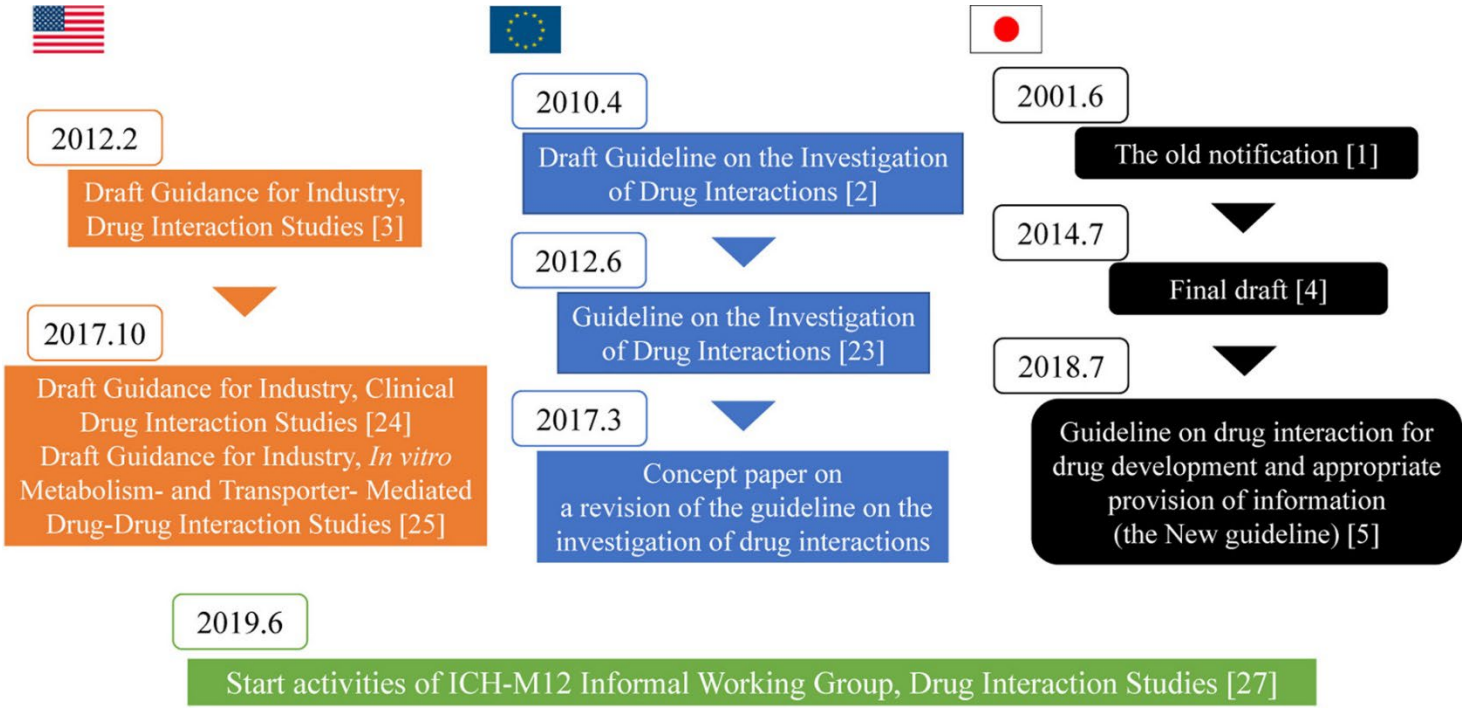
Outline

- Introduction
- PGx based medicine approved in Japan
- PMDA's activity related to PGx/BM
- Emerging topics

Emerging topics

- Utilization of Endogenous Biomarker for assessment of DDI

International harmonization on drug interaction studies

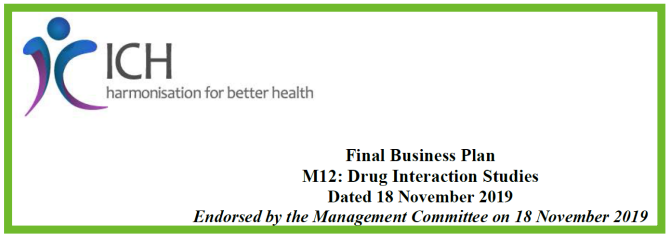


Drug Metab Pharmacokin 2020; 35: 12-17

Emerging topics

- Utilization of Endogenous Biomarker for assessment of DDI

M12 Concept paper



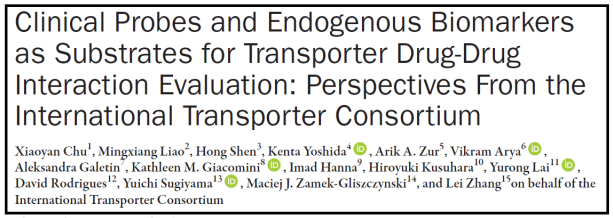
https://www.ich.org/page/multidisciplinary-guidelines

- The first ICH guideline on drug interaction studies
- The DDIs of interest for this harmonization effort are PK-driven and mediated by drug metabolizing enzymes and transporters
  - ✓ *In vitro* studies
  - ✓ Clinical DDI studies
  - ✓ Physiology-Based Pharmacokinetic (PBPK) Approaches
- **One of the issue for incorporating the latest scientific findings into M12 is the use of endogenous substrates in the assessment of transporter-mediated drug interaction**

Emerging topics

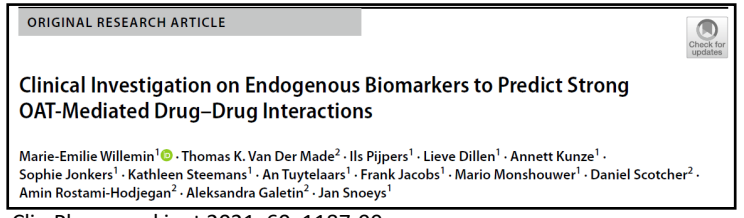
Utilization of Endogenous Biomarker for assessment of DDI

- Limitations in assessment of drug transport variability based on changes in drug concentrations in peripheral blood
- Interpretation of possible transporter-mediated drug interaction
  - ✓ Use of metabolite markers and pharmacodynamic markers reflecting changes in distribution to transporter-expressing organs
  - ✓ Evaluation of changes in exposure of endogenous substrates when the test drug is administered, which could be used to assess transporter-mediated drug interaction


Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium

Xiaoyan Chu[1], Mingxiang Liao[2], Hong Shen[3], Kenta Yoshida[4], Arik A. Zur[5], Vikram Arya[6], Aleksandra Galetin[7], Kathleen M. Giacomini[8], Imad Hanna[9], Hiroyuki Kusuhara[10], Yurong Lai[11], David Rodrigues[12], Yuichi Sugiyama[13], Maciej J. Zamek-Gliszczynski[14], and Lei Zhang[15] on behalf of the International Transporter Consortium

Clin Pharmacol Ther 2018; 104: 836-64


ORIGINAL RESEARCH ARTICLE

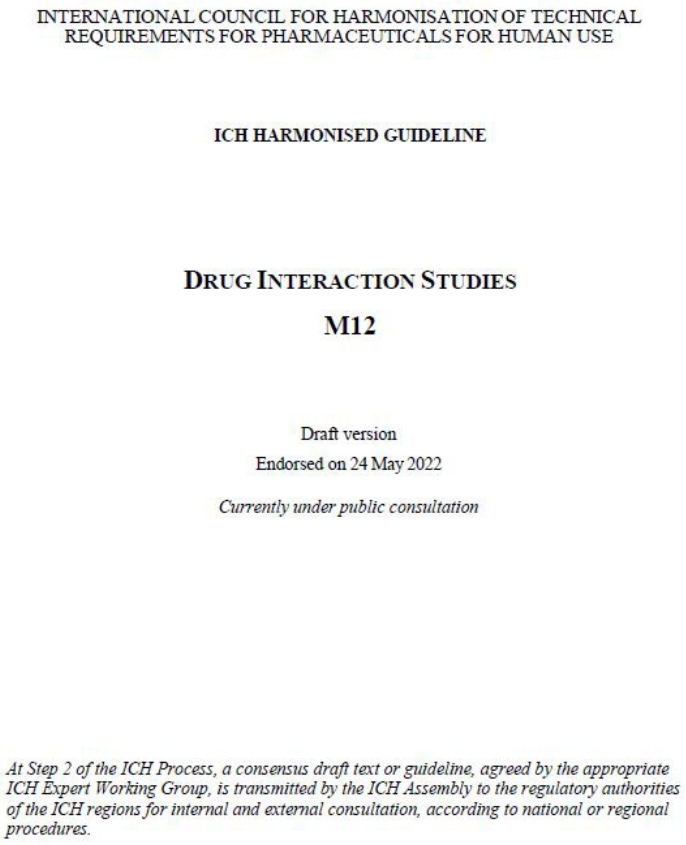
Clinical Investigation on Endogenous Biomarkers to Predict Strong OAT-Mediated Drug–Drug Interactions

Marie-Emilie Willemin[1] · Thomas K. Van Der Made[2] · Ils Pijpers[1] · Lieve Dillen[1] · Annett Kunze[1] · Sophie Jonkers[1] · Kathleen Steemans[1] · An Tuytelaars[1] · Frank Jacobs[1] · Mario Monshouwer[1] · Daniel Scotcher[2] · Amin Rostami-Hodjegan[2] · Aleksandra Galetin[2] · Jan Snoeys[1]

Clin Pharmacokinet 2021; 60: 1187-99

Emerging topics

- Utilization of Endogenous Biomarker for assessment of DDI



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

ICH HARMONISED GUIDELINE

DRUG INTERACTION STUDIES

M12

Draft version

Endorsed on 24 May 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

2.2.2 Drug as an Inhibitor of Transporters

…If the above analysis indicates that a drug inhibits a transporter, a clinical study should be considered based on whether the likely concomitant medications used in the indicated patient populations are known substrates of the inhibited transporter and the safety profiles of those substrates. Alternatively, the inhibition potential of a drug can be evaluated using mechanistic static models, PBPK modeling, or endogenous biomarkers. These approaches should be supported by submission of evidence supporting validity of the methods.

Future perspective

- Continue to enhance consultation system and regulatory activities for developing guideline to facilitate proper use of PGx/BMs into drug development.
- Improve environment around PGx-based medicine including companion diagnostics to enable patients easily access to PGx-based medicine.
- Facilitate collaborations with academia, industries and regulatory agencies, and international harmonization.