我國藥品真實世界數據/證據推動進展

食品藥物管理署 劉佳萍科長

2021.06.23

衛生福利部
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Taiwan Food and Drug Administration
http://www.fda.gov.tw/

演講大綱

01 真實世界數據及真實世界證據定義及重要性

02 真實世界數據及真實世界證據國內外相關指引

03 國內真實世界數據及真實世界證據藥品相關指引簡介

04 國內外真實世界證據應用案例介紹

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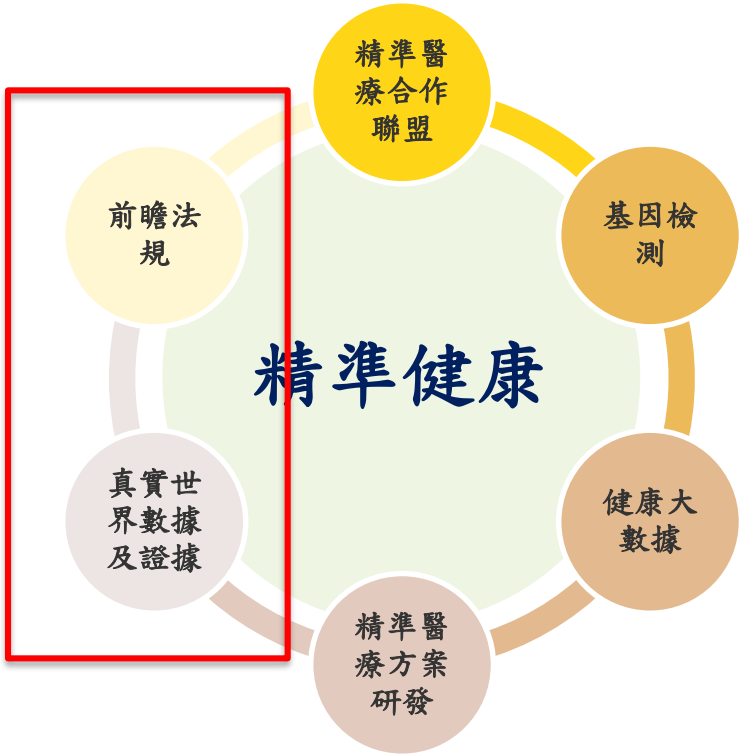
衛福部推動精準健康照護體系

- 配合2019 BTC委員總體建議，**推動建置「國家級生物資料庫整合平臺」**，發展我國精準醫療及個體化醫療產業研發環境，**引入真實世界證據及精準醫療之法規科學研究**，藉以達到跨域合作引領產業創新及法規布局帶動產業發展之政策目標。
- **於藥品研發過程中納入RWD/RWE策略，減少藥品研發成本，縮短藥品研發上市期程，創造互利多贏的局面。**



真實世界數據/真實世界證據重要性

- 以往藥品審查多依賴源自傳統隨機分派、對照性臨床試驗的療效與安全性證據，傳統臨床試驗雖有利推論藥品與療效、安全性之間的因果關係，**然其試驗結果外推性較低，且試驗規劃、執行需耗費較多的時間與成本，因此，引用來自真實世界的證據可輔助傳統臨床試驗在藥品研發的侷限性。**

- **又因應大數據、資料庫的發展**，真實世界證據為國際最新臨床應用趨勢，**於藥品研發過程納入RWD/RWE策略，期望可減少藥品研發成本，縮短藥品研發上市期程。**

真實世界數據(RWD)/真實世界證據(RWE)

Real-World Data (RWD)
真實世界數據

定義：
常規性蒐集(routinely collect)與病人健康狀態相關或來自於健康照護過程所得之多種數據*

Real-World Evidence (RWE)
真實世界證據

定義：
於一定的研究假設之下，使用真實世界數據為資料來源，經適當分析方法產生的臨床證據，此證據得用於協助說明藥品之使用及其效益風險*

RWD來源

- 電子健康紀錄
- 健康保險給付資料庫
- 藥品上市後研究或登記資料庫
- 疾病資料庫
- 居家生理監測資料、穿戴式裝置等

RWD轉換成RWE之考量

- 是否有足夠的關聯性
- 是否有足夠的可靠性
- 是否能確保數據品質
- 是否有適當的統計分析方法

RWE適用範疇

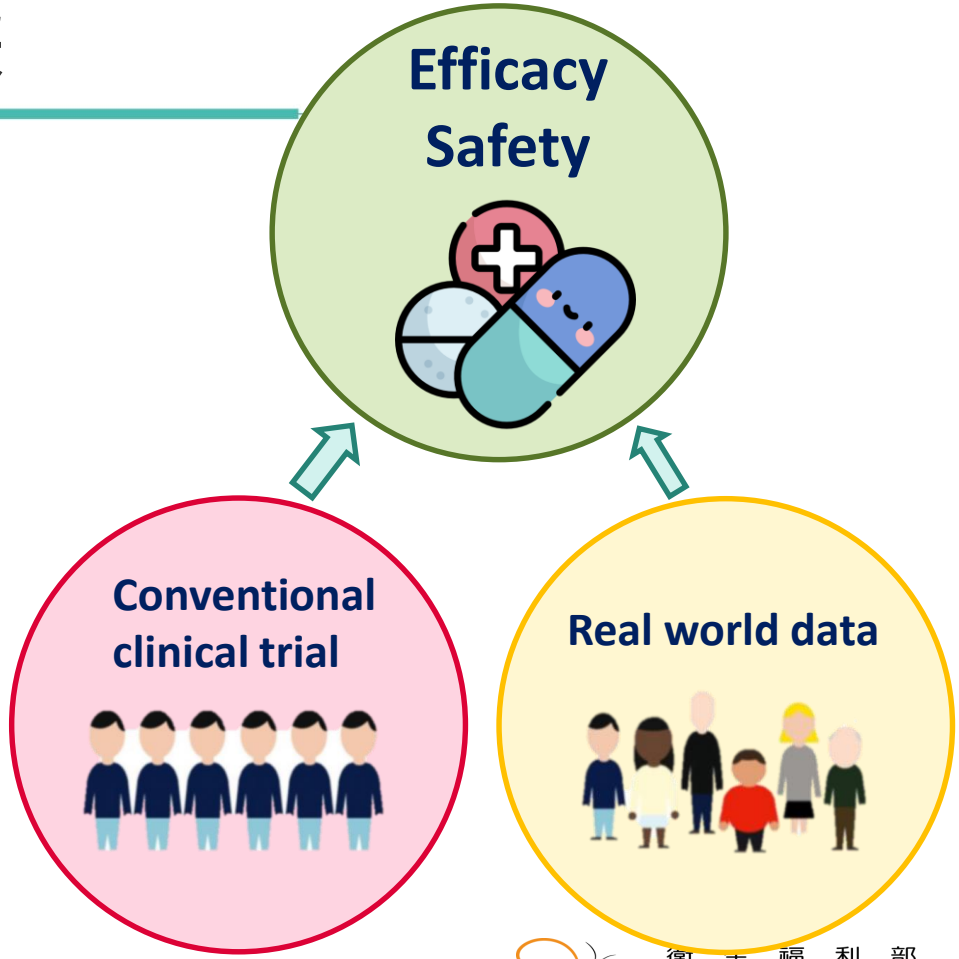
- 精進及輔助臨床試驗設計
- 藥品上市前的療效證據輔助 (例如專案進口)
- 藥品上市後的監視及安全性評估
- 上市後其他仿單資訊變更

* Reference: Framework for FDA' s Real-World Evidence Program, US FDA, 2018

真實世界證據

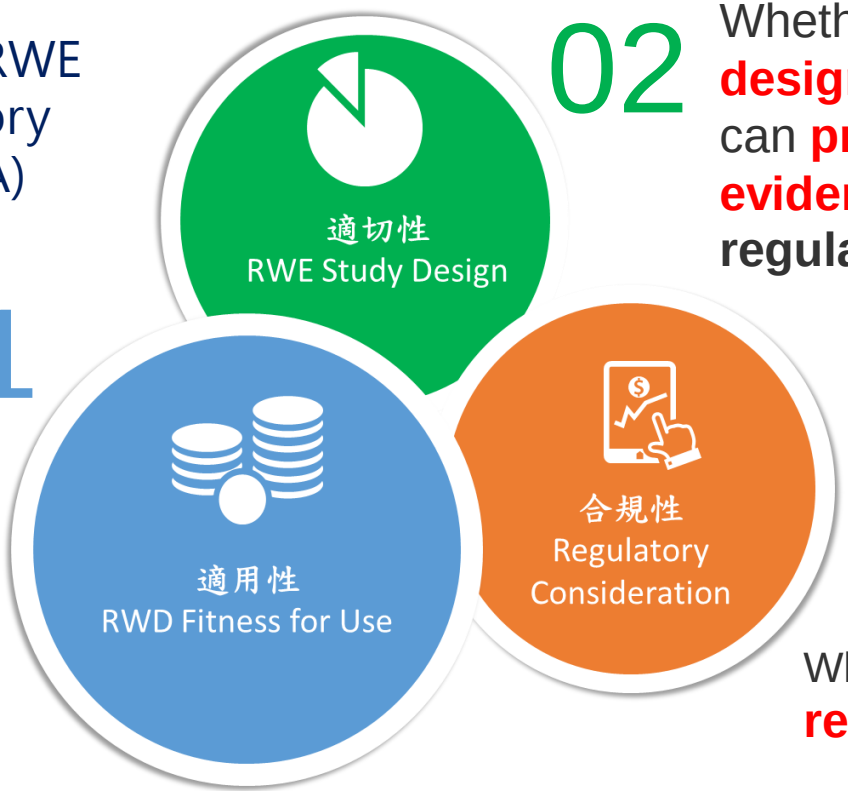
真實世界證據無法取代傳統隨機分派臨床試驗。

而是作為**輔助性證據**，彌補傳統臨床試驗於藥品研發之侷限。



真實世界數據/證據於查驗登記決策的評估框架

Framework for Evaluating RWD/RWE for use in regulatory decisions (US-FDA)



01

Whether the RWD are **fit for use**

02

Whether the **trial or study design** used to generate RWE can **provide adequate scientific evidence** to answer the **regulatory question**

03

Whether the study conduct meets **regulatory requirements**

* Reference: Framework for FDA's Real-World Evidence Program, US FDA, 2018

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訂定真實世界數據/真實世界證據指引

- 各國皆重點推動真實世界證據的發展，**國際上許多法規單位致力於產出相關指引或指導文件**，讓業界能了解法規單位對於RWD/RWE的政策及審查考量。
- 目前國內業界對於真實世界證據的應用發展尚不熟悉，**本署參考國際間已公布之指引，並納入國內情形，所研擬的指引為參考性**，提供業界對於真實世界證據的應用有所了解依循。
- 指引內容係針對RWE策略適用性考量、真實世界研究設計、真實世界數據的關聯性和數據品質，以及統計分析方法等重點進行探討。

國際間真實世界數據/證據指引參考

美國FDA

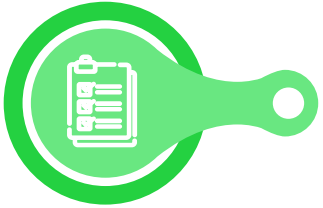
1. Framework for FDA's Real-World Evidence Program (2018)
2. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (2019)

歐盟EMA

Scientific Guidance on Post-Authorization Efficacy Studies (2016)

加拿大 Health Canada

Optimizing the Use of RWE to Inform Regulatory Decision-Making (2019)



日本MHLW

1. Basic principles on Utilization of Registry for Applications (2021)
2. Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications (2021)

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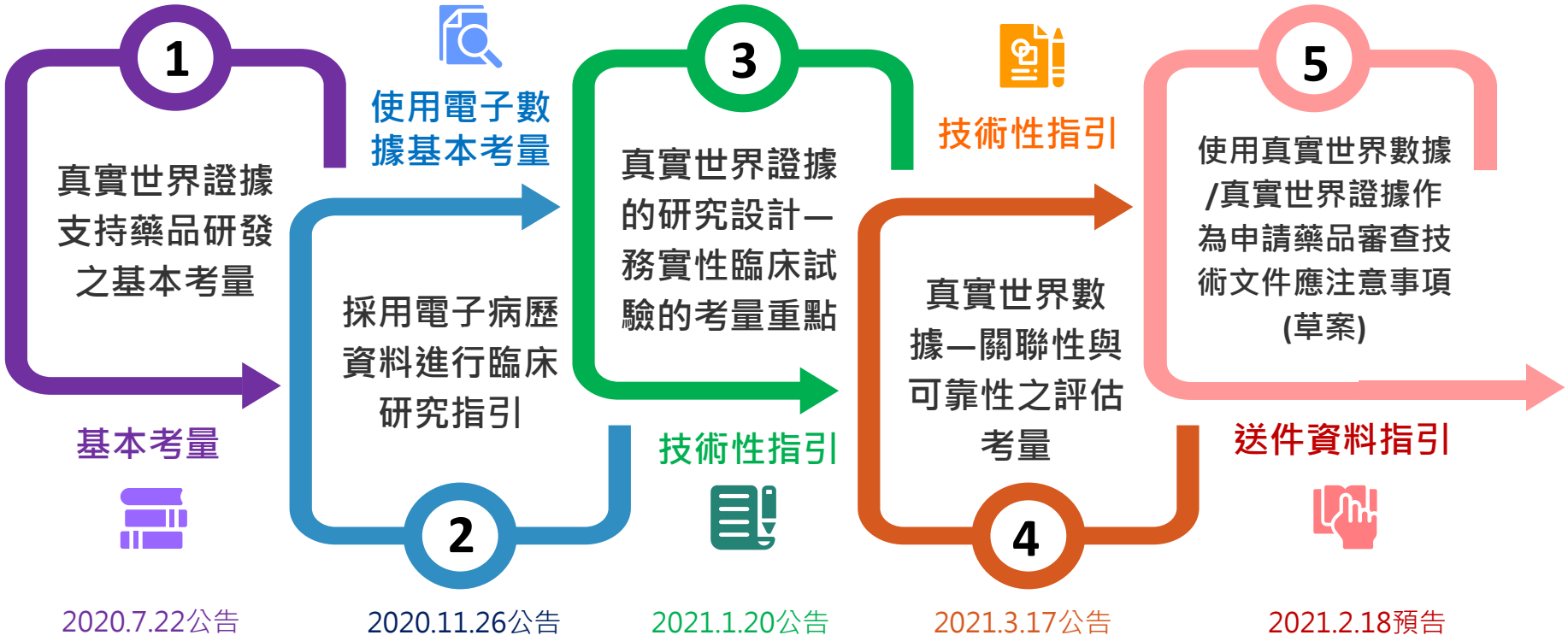
藥品真實世界數據/證據指引訂定

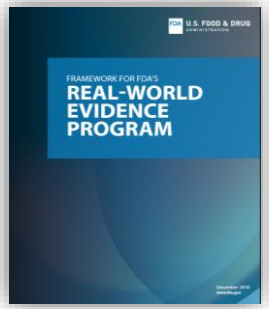


1

真實世界證據支持藥品研發之基本考量

2020.07.22公告

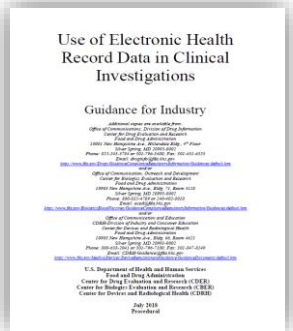
- **指引目的：**
  - 提供研究者對真實世界證據(RWE)用於藥品研發之建議。
  - 說明法規單位對於此類研究設計及研究方法之基本考量。
- **指引內容重點：**
  - 定義何謂真實世界數據(RWD)及真實世界證據(RWE)。
  - 說明應如何產出良好品質的RWE。
  - 針對RWD的收集流程及研究方法設計提出考量及建議。
- **參考依據：**Framework for FDA’ s Real-World Evidence Program (US FDA)



2

採用電子病歷資料進行臨床研究指引

2020.11.26公告


Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

- **指引目的：**
  - 促進試驗研究者在臨床研究中使用電子病歷資料
  - 推動電子病歷資料與電子資料擷取系統間的可交互運作性
- **指引內容重點：**
  - 就臨床研究使用電子病歷資料提出下列考量建議：
    - 系統間的可交互運作性與整合、使用電子病歷資料進行研究之最佳操作、查核、記錄與文件保存之要求
  - 臨床研究運用電子病歷的最佳實務
- **參考依據：**Use of Electronic Health Record Data in Clinical Investigations (US FDA)

3

真實世界證據的研究設計—務實性臨床試驗的考量與重點

2021.1.20公告

- **指引目的：**
  - ✓ 延續「真實世界證據支持藥品研發之基本考量」
  - ✓ 針對其他能產生真實世界數據的研究方式提出簡要說明，著重在務實性臨床試驗設計的考量與重點。
- **指引內容重點：**
  - ✓ 著重於務實性臨床試驗的特色
  - ✓ 評估臨床試驗的務實性程度
  - ✓ 務實性臨床試驗的設計方法

4

真實世界數據—關聯性與可靠性之評估考量

2021.3.17公告

- **指引目的：**
  - ✓ 如何評估RWD數據的關聯性與可靠性
  - ✓ 針對常見的數據來源，如電子健康紀錄、健康保險給付資料庫以及經由病人產生的數據(如穿戴式行動裝置或居家照護生理監測系統)，分別討論其關聯性與數據品質特徵

- **指引內容重點：**
  - ✓ 闡述RWD適用性，並參酌國際相關指引，提出數據關聯性和數據可靠性的評估建議。

5

使用真實世界數據/真實世界證據作為申請藥品審查技術文件應注意事項(草案)

2021.02.18預告

- **指引目的：**
  - ✓ 以「真實世界證據支持藥品研發之基本考量」等指引為基礎，作為藥品審查技術文件之參考依循。
- **指引內容重點：**
  - ✓ 適用範疇：藥品臨床試驗/研究申請案、新藥查驗登記申請案、藥品上市後變更申請案、藥品上市後要求。
  - ✓ 敘明申請者應檢附作為審查之評估資料及法規單位之審查依據。
- **參考依據：**Submitting documents using real-world data and real-world evidence to FDA for drugs and biologics (US FDA)

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1

案例一 罕見疾病藥品上市前療效證據

Sapropterin dihydrochloride

- BH4缺乏導致之高苯丙胺酸血症 (Hyperphenylalaninemia due to tetrahydrobioterin deficiency)
- 查登前已依「罕見疾病防治及藥物法」專案進口使用
- 查登時檢送國內兩家醫學中心之回溯性觀察性研究
  - National Taiwan University Hospital； 14 patients; 3-20 years
  - Taipei Veterans General Hospital； 21 patients; >10 years

2

案例二 發生率較低癌症單臂試驗外部對照

Pralatrexate

- 治療復發或頑固型周邊T細胞淋巴瘤 (peripheral T-cell lymphoma, PTCL)。
- 樞紐試驗採開放性、單臂設計。
- 利用國外四個醫療中心之病歷資料，與臨床試驗收納之受試者執行配對，並分析配對病人接受其他治療後之整體存活率，做為Pralatrexate單臂試驗之外部對照組。

3

案例三 上市後監視及安全性評估

1. 廢止含 ketoconazole成分的口服抗黴菌藥品之藥品許可證 (肝毒性)。
2. 評估抗凝血藥品dabigatran治療相較於warfarin的出血風險。(US FDA)
3. 藉由使用上市後研究之結果，評估輪狀病毒口服疫苗使用與腸套疊的關聯性。(US FDA)

4

案例四 上市後擴增適應症(US FDA)

Ibrance (palbociclib)

- **Adult patients** with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with
  - an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women **or in men;** or
  - fulvestrant in **patients** with disease progression following endocrine therapy
- Flatiron Health (EHR), IQVIA (medical claims), Pfizer Global Safety Database

謝謝聆聽

欣耀生醫
SINEW PHARMA

美國FDA體外藥品交互作用最新指引

熊正輝 博士
欣耀生醫副總經理

2021.06.23

欣耀生醫
SINEW PHARMA

Outline

- **Evolution of FDA DDI Guidances**
- **2020 DDI Guidances**
  - **Scope**
  - **Goal: From *in vitro* to *in vivo***
  - ***In vitro* DDI Evaluation**
    - **NME as Substrate**
    - **NME as inhibitor**
    - **NME as inducer**
  - **DDI potential of Metabolites**

Evolution of FDA DDI Guidances

- 1997 (In vitro)
- 1999 (In vivo)
- 2006 (Draft; In vitro and In vivo)
  - P-gp
  - Detailed appendices- methodology
- 2012 (Draft; In vitro and In vivo)
  - More transporters
  - Model-based DDI evaluations
  - Labeling recommendations
  - Removed the appendices
- 2017 (Draft)
  - Two separate guidances: in vitro and in vivo (clinical)
  - In vitro guidance includes appendices
- 2020 Final

Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

2020 DDI Guidances: Scope

- Scope: Evaluation of cytochrome P450 (CYP) or transporter mediated DDIs
- Topics not addressed in the 2020 guidances
  - **Therapeutic protein DDIs**
  - **Gastric pH change-dependent DDIs**
  - **DDIs involving oral contraceptives**
  - **Protein displacement-mediated DDIs**
  - **Phase II enzyme-mediated DDIs**
  - **Pharmacodynamic DDIs**
  - **Detailed guidance on product labeling language**

Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

From *in vitro* and *in vivo*

- In vitro Guidance
  - Define the potential for DDI of an investigational drug as substrate or perpetrator
  - Help determine when and which clinical DDI assessments are needed

Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

In Vitro Evaluation – NME As Substrates

- Metabolic phenotyping: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A
- If the above CYP enzymes do not play a major role, consider other enzymes
  - CYP2A6, CYP2J2, CYP4F2, and CYP2E1
  - Other Phase I enzymes including aldehyde oxidase (AO), carboxylesterase
  - (CES), monoamine oxidase (MAO), flavin monooxygenase (FMO), xanthine oxidase (XO), and alcohol/aldehyde dehydrogenase (ADH/ALDH)
  - Phase II enzymes, e.g., UDP glucuronosyl transferases (UGTs) and sulfotransferases (SULTs)
- If ≥25% clearance by an enzyme (in vitro phenotyping; human PK), need to consider further clinical evaluation, i.e., evaluate effect of inhibitor and inducer of the enzyme on the PK of the NME

Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

In Vitro Study – NME As Substrates

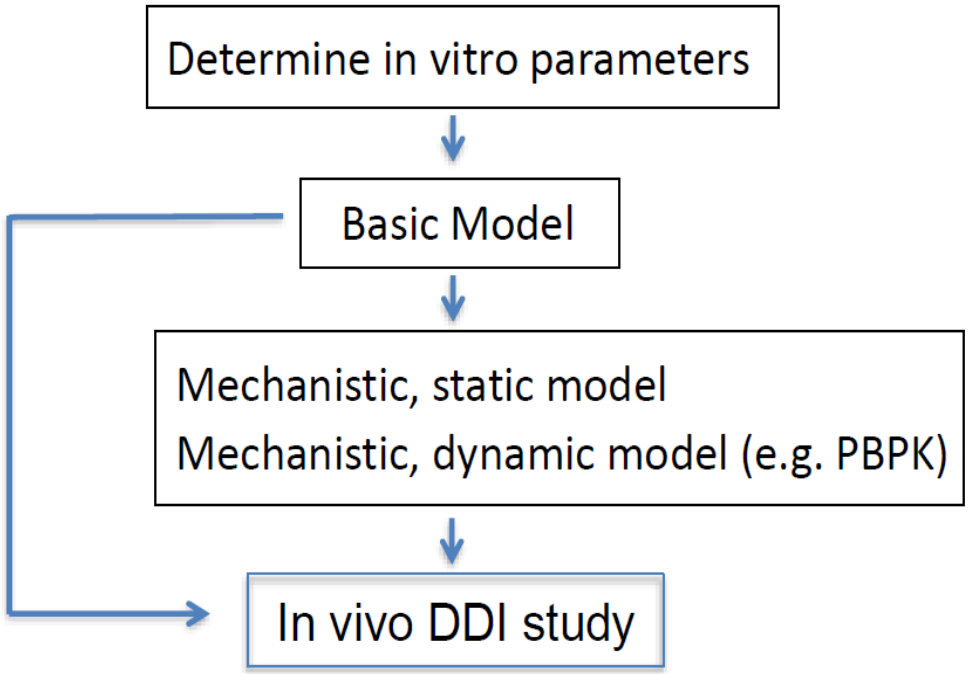
- System: S9, cytosol, rCYP, pooled human liver microsomes(HLM), Human Hepatocytes
- Metabolic pathway identification (ID) before first in human (FIH)
- Use both chemical/antibodies inhibitors with HLM & rCYPs
- Identify number and structures of metabolites produced
- Robust and reproducible methods with appropriate positive controls

Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

Determine if NME is an Inhibitor or Inducer of Metabolic Enzymes

CYP inhibitor
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A)

CYP inducer
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4)



Reynolds KS and Yang X, Updated on FDA's Drug-Drug Interaction Final Guidances, FDA Webinars, April 24, 2020.

Basic Model for Reversible Inhibition

$$R = \frac{AUC_{\ with\ inhibitor}}{AUC_{\ no\ inhibitor}}$$

$$R_1 = 1 + (I_{max,u} / K_i)$$

$$R_{1,gut} = 1 + (I_{gut} / K_i)$$

R_1 or **$R_{1,\ gut}$** is the predicted ratio of the victim drug's AUC in the presence and absence of an inhibitor for basic models of reversible inhibition.
$I_{max,u}$ is the maximal unbound plasma concentration of the interacting drug.*
I_{gut} is the intestinal luminal concentration of the interacting drug calculated as the dose/250 mL.
K_i is the unbound inhibition constant determined in vitro.

Note: I and K_i need to be expressed in the same unit (e.g., in a molar concentration unit).

*Considering uncertainties in the protein binding measurements, the unbound fraction in plasma should be set to 1% (fraction unbound in the plasma ($f_{u,p}$) = 0.01) if experimentally determined to be < 1%.

$$E + I \underset{k-1}{\overset{k1}{\rightleftharpoons}} E : I \qquad K_i = k_{\_1}/k_1$$

Mechanistic Static Model for Reversible Inhibition

$$AUCR = \frac{1}{A_H \times fm + (1 - fm)} \times \frac{1}{A_g \times (1 - Fg) + Fg}$$

$$A_H = \frac{1}{1 + \frac{[I]_H}{K_i}}, A_g = \frac{1}{1 + \frac{[I]_g}{K_i}}$$

A is the effect of reversible inhibitions.
F_g is the fraction available after intestinal metabolism.
f_m is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition.
Subscripts 'H' denote liver.
Subscripts 'g' denote gut.

$[I]_h = f_{u,p} \times (C_{max} + F_a \times k_a \times Dose/Q_h/R_B)$ (Ito, Iwatsubo, et al. 1998)
$[I]_g = F_a \times k_a \times Dose/Q_{en}$ (Rostami-Hodjegan and Tucker 2004)

$f_{u,p}$ is the unbound fraction in plasma. When it is difficult to measure accurately due to high protein binding (i.e., $f_{u,p}$ <0.01) in plasma, a value of 0.01 should be used for $f_{u,p}$.
C_{max} is the maximal total (free and bound) inhibitor concentration in the plasma at steady state.
F_a is the fraction absorbed after oral administration; a value of 1 should be used when the data are not available.
k_a is the first order absorption rate constant in vivo; a value of 0.1 min^{-1} (Ito, Iwatsubo, et al. 1998) can be used when the data are not available.
Q_{en} is the blood flow through enterocytes (e.g., 18 L/hr/70 kg (Yang, Jamei, et al. 2007a)).
Q_h is the hepatic blood flow (e.g., 97 L/hr/70 kg (Yang, Jamei, et al. 2007b)).
R_B is the blood-to-plasma concentration ratio.

Determining If Investigational Drug Is Reversible Inhibitor Of Metabolizing Enzymes

In-vitro investigation for the major CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4/5

Data Analysis:

1. Basic Model
   - $R_I = 1 + (I_{max,u} / K_i)$
   - $R_{I,gut} = 1 + (I_{gut} / K_i)$ where I_{gut}=dose/250 mL
2. AUCR prediction [using inhibition data only] by:
   - Mechanistic Static Model

$$AUCR = \left[\frac{1}{C_H X f_m + (1 - f_m)} X \frac{1}{C_G X (1 - f_G) + f_G} \right]$$

$$C = \frac{1}{1 + \frac{[I]}{K_i}}$$

   - Dynamic Mechanistic Model such as PBPK Model
3. *In-Vivo* Studies using a sensitive index substrate

Data Interpretation

If $R_I \geq 1.02$

Or $R_{I,gut} \geq 11$

↓

If AUCR ≥ 1.25

↓

Conduct a clinical DDI

Basic Model for Time-dependent Inhibition

$$R = \frac{AUC_{with\ inhibitor}}{AUC_{no\ inhibitor}}$$

$$E + I \underset{k-1}{\overset{k1}{\rightleftharpoons}} E:I \xrightarrow{k_{inact}} E:I^*$$

k_{inact} describes the rate at which the inhibitor-enzyme complex is irreversibly transformed into E:I*

$$R_2 = (k_{obs} + k_{deg}) / k_{deg}$$

$$\text{Where } k_{obs} = (k_{inact} \times 50 \times I_{max,u}) / (K_I + 50 \times I_{max,u})$$

$$K_I = k_{-1} / k_1$$

R_2 is the predicted ratio of the victim drug's AUC in the presence and absence of an inhibitor for basic models of enzyme TDI.
k_{obs} is the observed (apparent first order) inactivation rate constant of the affected enzyme.
k_{deg} is the apparent first-order degradation rate constant of the affected enzyme.
K_I is the inhibitor concentration causing half-maximal inactivation.
k_{inact} is the maximal inactivation rate constant.
$I_{max,u}$ is the maximal unbound plasma concentration of the interacting drug.*

Note: I and K_I need to be expressed in the same unit (e.g., in a molar concentration unit).

*Considering uncertainties in the protein binding measurements, the unbound fraction in plasma should be set to 1% (fraction unbound in the plasma ($f_{u,p}$) = 0.01) if experimentally determined to be < 1%.

Mechanistic Static Model for Time-dependent Inhibition

$$AUCR = \frac{1}{B_H \times fm + (1 - fm)} \times \frac{1}{B_g \times (1 - Fg) + Fg}$$

$$B_H = \frac{k_{deg,H}}{k_{deg,H} + \frac{[I]_H \times k_{inact}}{[I]_H + K_i}}$$

$$B_g = \frac{k_{deg,g}}{k_{deg,g} + \frac{[I]_g \times k_{inact}}{[I]_g + Ki}}$$

B is the effect of TDI.
F_g is the fraction available after intestinal metabolism.
f_m is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition.
Subscripts 'H' denote liver.
Subscripts 'g' denote gut.
K_{deg} is the enzyme degradation rate.
K_{inact} is the first-order inactivation rate constant of the enzyme.

$[I]_h = f_{u,p} \times (C_{max} + F_a \times k_a \times Dose/Q_h/R_B)$ (Ito, Iwatsubo, et al. 1998)
$[I]_g = F_a \times k_a \times Dose/Q_{en}$ (Rostami-Hodjegan and Tucker 2004)
$f_{u,p}$ is the unbound fraction in plasma. When it is difficult to measure accurately due to high protein binding (i.e., $f_{u,p}$ <0.01) in plasma, a value of 0.01 should be used for $f_{u,p}$.
C_{max} is the maximal total (free and bound) inhibitor concentration in the plasma at steady state.
F_a is the fraction absorbed after oral administration; a value of 1 should be used when the data are not available.
k_a is the first order absorption rate constant in vivo; a value of 0.1 min^{-1} (Ito, Iwatsubo, et al. 1998) can be used when the data are not available.
Q_{en} is the blood flow through enterocytes (e.g., 18 L/hr/70 kg (Yang, Jamei, et al. 2007a)).
Q_h is the hepatic blood flow (e.g., 97 L/hr/70 kg (Yang, Jamei, et al. 2007b)).
R_B is the blood-to-plasma concentration ratio.

Determining If Investigational Drug Is Time-dependent Inhibitor Of Metabolizing Enzymes

In-vitro investigation for the major CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4/5

Data Analysis:

1. Basic Model

$$R_2 = (K_{obs} + K_{deg}) / K_{deg}$$

where $K_{obs} = (K_{inact} \times 50 \times I_{max,u}) / (K_I + 50 \times I_{max,u})$

2. AUCR prediction [using TDI data only] by:
   - Mechanistic Static Model

$$AUCR = \left[\frac{1}{A_h \times f_m + (1 - f_m)} \times \frac{1}{A_G \times (1 - f_G) + f_g} \right]$$

$$A = \left(\frac{k_{deg}}{k_{deg} + \frac{[I] \times k_{inact}}{[I] + K_I}} \right)$$

   - Dynamic Mechanistic Model such as PBPK Model
3. *In-Vivo* Studies using a sensitive index substrate

Data Interpretation

If $R_2 \geq 1.25$

↓

If AUCR ≥ 1.25

↓

Conduct a clinical DDI

In Vitro Study – NME As Inhibitors

- System: Pooled HLM (>10), recombinant CYP enzymes, or pooled hepatocytes (>10)
- HLM protein concentration should be < 1 mg/mL. Correct for binding when necessary
- Solvents should be <1%, 0.5% is preferred
- Include vehicle control & no-solvent control
- Validated & reproducible analytical assays and Positive controls kinetic constants (k_i, K_I and k_{inact}) should be comparable to literature

Reversible inhibition

- Initially, test drug at high concentration as much as possible

  e.g., 50 X $I_{max,u}$ or 0.1 X dose/250 mL
- If positive, then retest to calculate IC_{50} or k_i

TDI:

- Initially, preincubate drug for at least 30 min before adding the substrate
- If significant time- and NADPH-dependent, then retest in a definitive study for estimation of K_I & k_{inact}

Determine if NME is an Inducer of CYP Enzymes

- Evaluate CYP1A2, CYP2B6, and CYP3A4 initially.
- If no induction of CYP3A4 is observed, evaluating the induction potential of **CYP2C enzymes** not needed because CYP3A and CYP2C enzymes are induced via activation of the pregnane X receptor (PXR) and **CYP3A is more sensitive to inducer.**
- If the drug induces CYP3A4, evaluate the drug's potential to induce CYP2C enzymes.

Evaluate Induction Potential of CYPs - Basic Model

- **Fold-change method**
  - using a cutoff determined from known positive and negative controls
  - Ex: a ≥ 2-fold increase in mRNA and a response ≥ 20% of the response of the positive control
- **Correlation methods**
  - Method 1: Calculate a relative induction score (RIS) using $(E_{max} \times I_{max,u}) / (EC_{50} + I_{max,u})$
  - Method 2: Calculate $I_{max,u} / EC_{50}$ values

Evaluate Induction Potential of CYPs - Basic Kinetic Model

$$R = \frac{AUC_{\,with\ inducer}}{AUC_{\,no\ inducer}}$$

$$R_3 = 1 / [1 + (d \times E_{max} \times 10 \times I_{max,u}) / (EC_{50} + (10 \times I_{max,u}))]$$

R_3 is the predicted ratio of the victim drug's AUC in the presence and absence of an inducer for basic models of enzyme induction.
d is the scaling factor and is assumed to be 1 unless supported by prior experience with the system used.
E_{max} is the maximum induction effect determined in vitro.
$I_{max,u}$ is the maximal unbound plasma concentration of the interacting drug.*
EC_{50} is the concentration causing half-maximal effect determined in vitro.

*Considering uncertainties in the protein binding measurements, the unbound fraction should be set to 1% if experimentally determined to be <1%.

Evaluate Induction Potential of CYPs - Mechanistic Static Model

$$AUCR = \frac{1}{C_H \times fm + (1 - fm)} \times \frac{1}{C_g \times (1 - Fg) + Fg}$$

$$C_H = 1 + \frac{d \times E_{max} \times [I]_H}{[I]_H + EC_{50}} \qquad C_g = 1 + \frac{d \times E_{max} \times [I]_g}{[I]_g + EC_{50}}$$

C is the effect of induction.

$\mathbf{F_g}$ is the fraction available after intestinal metabolism.

$\mathbf{f_m}$ is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to induction.

Subscripts 'H' denote liver.

Subscripts 'g' denote gut.

$[I]_h = f_{u,p} \times (C_{max} + F_a \times k_a \times Dose/Q_h/R_B)$ (Ito, Iwatsubo, et al. 1998)

$[I]_g = F_a \times k_a \times Dose/Q_{en}$ (Rostami-Hodjegan and Tucker 2004)

$\mathbf{f_{u,p}}$ is the unbound fraction in plasma. When it is difficult to measure accurately due to high protein binding (i.e., f_u <0.01) in plasma, a value of 0.01 should be used for $f_{u,p}$.

$\mathbf{C_{max}}$ is the maximal total (free and bound) inhibitor concentration in the plasma at steady state.

$\mathbf{F_a}$ is the fraction absorbed after oral administration; a value of 1 should be used when the data are not available.

$\mathbf{k_a}$ is the first order absorption rate constant in vivo; a value of 0.1 min^{-1} (Ito, Iwatsubo, et al. 1998) can be used when the data are not available.

$\mathbf{Q_{en}}$ is the blood flow through enterocytes (e.g., 18 L/hr/70 kg (Yang, Jamei, et al. 2007a)).

$\mathbf{Q_h}$ is the hepatic blood flow (e.g., 97 L/hr/70 kg (Yang, Jamei, et al. 2007b)).

$\mathbf{R_B}$ is the blood-to-plasma concentration ratio.

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Determining if Investigational Drug is an Inducer of CYP Enzymes

In-vitro investigation for the major CYP enzymes CYP1A2, CYP2B6 & CYP3A4/5

- Basic Model
  - Fold Change Method (pre-established cutoff, of fold induction, % relative to PC)
  - Correlation methods (RIS OR ** $I_{max,u}$ / EC_{50})
- Basic Kinetic Model

  $R3 = 1/[1+(d \times E_{max} \times (10 \times I_{max,u}) / (EC_{50} + (10 \times I_{max,u}))]$
- AUCR prediction [analyze induction data only] by:
  - Mechanistic Static Model]

$$AUCR = \left[\frac{1}{C_H \times f_m + (1-f_m)} \times \frac{1}{C_G \times (1-f_G) + f_G} \right]$$

$$C = 1 + \frac{d \times E_{max} \times [I]}{[I] + EC_{50}}$$

  - Dynamic Mechanistic Model such as PBPK Model
- If no CYP3A4/5 induction, then evaluation of CYP2C8/2C9/2C19 is not necessary

Preset Cutoff

↓

R3 ≤ 0.8

↓

AUCR ≤ 0.8

↓

Conduct a clinical DDI using a sensitive index substrate

In Vitro Study – NME As Inducers

- System: Plateable, cryopreserved or freshly isolated, **human hepatocytes from at least 3 donors**
  - Immortalized hepatic cell lines could be used also
  - Cell receptor assays results are considered supportive and not definitive
- mRNA and/or enzyme activity levels are acceptable. If **TDI, then mRNA approach is recommended**
- *In vitro* test system should be validated to **show that all major 6 CYPs are functional and inducible with positive controls**. System should be robust and reproducible
- Drug concentrations investigated should span the range of therapeutic exposures. If the drug solubility permits, this range of drug concentrations should include **at least one concentration that is an order of magnitude greater than the maximum unbound steady-state plasma drug concentration** *in vivo*
- Measure concentrations of the actual **unbound parent drug in the medium**
  - If the drug is **highly bound** to human plasma protein, and the medium contains serum (or proteins, e.g., bovine serum albumin)
  - if the drug may have **significant non-specific binding**

Additional Considerations

Investigational drug is an inhibitor of **multiple CYP enzymes**

- may first carry out an ***in vivo* study** with a sensitive index substrate of the CYP with the **largest R or AUCR value**
  - If this *in vivo* study shows **no interaction**, *in vivo* evaluations of other CYPs with **lower potencies** (e.g., smaller R or AUCR) **are not needed**.
  - if this *in vivo* study shows a **positive interaction** between the drug and the sensitive index CYP substrate, the sponsor should conduct additional *in vivo* studies for other CYPs, starting with the CYP with the **next largest R or AUCR value**.

DDI Potential of Metabolites

- **As a substrate**: for metabolites with safety concern or significantly contributing to overall efficacy (estimated based on potency, protein binding, tissue distribution of metabolites relative to parent)
- **As an inhibitor**:
  - for metabolites **more polar** than parent: $AUC_{metabolite} \geq AUC_{parent}$
  - for metabolites **less polar** than parent: $AUC_{metabolite} \geq 25\% \times AUC_{parent}$
  - for metabolite that acts as **time-dependent inhibitor** (TDI), consider a lower exposure than parent
  - Exposure comparison based on **Molar units**!

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美國/歐盟/日本體外藥品交互作用法規比較

熊正輝 博士
欣耀生醫副總經理

2021.06.23

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Outline

- **Evolution of DDI Guidances of FDA, EMA and PMDA**
- **CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines**
- **Conclusions**

Evolution of DDI Guidances of FDA, EMA and PMDA

ITC (International Transporter Consortium) continue discussions on transporter-mediated interactions started in 2010 with publication Membrane Transporters in Drug Development

ITC further discuss aspects of transporter-mediated interactions and later publishes Summarizing Advances in the Role of Transporters in Drug Development In 2018

FDA publish draft guidance


In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies
Guidance for Industry

FDA publish final DDI guidance for in vitro and clinical studies


In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions
Guidance for Industry


Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions
Guidance for Industry

2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020

EMA publish DDI guidance

EMA consultation on update to 2013 DDI guidance completed

PMDA Japanese 2018 DDI guidance published

EMA ongoing review of proposed updates to DDI guidance

Compare FDA guidance to EMA & PMDA for in vitro DDI assessments (covance.com)

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CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines(I)

Item	FDA 2020	EMA 2013	PMDA 2018
In vitro test system	Subcellular human liver tissue fractions, recombinant human CYP enzymes, human liver tissue, including freshly prepared or cryopreserved hepatocytes	Human liver microsomes or S9 fraction, recombinant human enzymes, and human hepatocytes	Human liver microsomes or S9 fraction, recombinant human enzymes, and human hepatocytes
Metabolic enzymes	**Major CYP enzymes**: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. **Additional CYP enzymes**: CYP2A6, CYP2J2, CYP4F2, and CYP2E1 **Other Phase I enzymes**: Aldehyde oxidase (AO), carboxylesterase (CES), monoamine oxidase (MAO), Flavin monooxygenase (FMO), Xanthine oxidase (XO), and alcohol//aldehyde dehydrogenase (ADH/ALDH). **Phase II enzymes**: UDP glucuronosyl transferases (UGTs) and sulfotransferase (SULTs).	**CYP and non-CYP enzymes**. Genetic polymorphic enzymes and special populations. Identification of enzymes involved in minor pathways may be needed if the pathways have a marked importance in some subpopulations due to intrinsic or extrinsic factors.	**Major CYP enzymes**: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. **Additional CYP enzymes**: CYP2A6, CYP2J2, CYP4F2, and CYP2E1 **Other Phase I enzymes**: monoamine oxidase (MAO), Flavin monooxygenase (FMO), Xanthine oxidase (XO), and alcohol//aldehyde dehydrogenase (ADH/ALDH). **Phase II enzymes**: UDP glucuronosyl transferases (UGTs).

CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines(II)

Item	FDA 2020	EMA 2013	PMDA 2018
NME As Substrates	Specific enzyme contributes to ≥25% of the drug's elimination based on in vitro data or human PK data should be identified.	Enzymes that are involved in metabolic pathways contributing to ≥25% of drug elimination should be identified if possible and the in vivo contribution should be quantified.	The in vivo contribution ratio (CR) of the elimination pathway controlled by a certain drug metabolizing enzyme to the overall elimination of the investigational drug is estimated to be ≥25% from in vitro metabolism studies and clinical pharmacokinetic Studies
Evaluate inhibition potential of metabolite	Metabolite with significant plasma exposure or pharmacological activities may need to be evaluated for its DDI potential. The in vitro enzyme inhibition study should be performed if: • The metabolite is less polar than parent and the $AUC_{metabolite}$ ≥25% of AUC_{parent}. • The metabolite is more polar than parent drug and the metabolite $AUC_{metabolite}$ ≥the parent AUC_{parent}. • A lower cutoff value for AUC ratio may also be considered for metabolites with structural alerts for potential mechanism-based inhibition.	It is recommended to investigate the enzyme inhibitory potential of phase I metabolites with an AUC both >25% of the parent drug AUC and >10% of the drug related exposure (radioactive moieties in the mass-balance study).	It is recommended to investigate the enzyme inhibitory potential of major metabolite when: • The metabolite is less polar than the parent drug and the metabolite AUC is ≥25% of the parent drug AUC. • The metabolite is more polar than the parent drug and the metabolite AUC is ≥100% of the parent drug AUC. • The metabolite contains a chemical structural alert(s) for TDI and the metabolite AUC is ≥25% of the parent drug AUC and is ≥10% of total AUC of drug-related substances.

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CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines(III)

Item	FDA 2020	EMA 2013	PMDA 2018
NME As Inducers: In vitro test system	Plateable, cryopreserved or freshly isolated, human hepatocytes. Immortalized hepatic cell lines may also be used and are acceptable methods to determine CYP induction potential.	Cultured hepatocytes (fresh or cryopreserved) are the preferred in vitro system for induction (and downregulation)in vitro studies. Minimally derived hepatocyte lines (e.g. HepaRG), nuclear receptor binding assays, or reporter gene assays are considered as supportive data only.	Cultured hepatocytes (fresh or cryopreserved) are the preferred in vitro system for induction (and downregulation)in vitro studies. Minimally derived hepatocyte lines (e.g. HepaRG), nuclear receptor binding assays, or reporter gene assays are considered as supportive data only.
NME As Inducers: CYP enzymes	Initial induction of CYP1A2, CYP2B6, and CYP3A4. CYP2C8, CYP2C9, CYP2C19 (when induction of CYP3A4 is observed).	Initial induction of CYP1A2, CYP2B6, and CYP3A4. CYP2C8, CYP2C9, CYP2C19 (when induction of CYP3A4 is observed).	Initial induction of CYP1A2, CYP2B6, and CYP3A (CYP3A4 and CYP3A5). CYP2C8, CYP2C9, CYP2C19 (when induction of CYP3A4 is observed).

CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines(IV)

Item	FDA 2020	EMA 2013	PMDA 2018
Fold-change method	A cutoff can be determined from known positive and negative controls to calibrate the system • ex) mRNA ≥ 2-fold & ≥20% of positive control	• mRNA ≥ 2-fold & concentration dependent changes • mRNA< 2-fold & ≥20% of positive control	A cutoff can be determined from known positive and negative controls to calibrate the system • mRNA ≥ 2-fold & concentration-dependent changes • mRNA< 2-fold & ≥ 20% of positive control
Correlation method	Method 1: Calculate a relative induction score (RIS) using $(E_{max} \times I_{max,u}) / (EC_{50}+I_{max,u})$ Method 2: Calculate $I_{max,u}/ EC_{50}$values	Predicted positive criteria defined by known positive controls can be used RIS: $E_{max} \times [I]/(EC_{50} +[I])$ [I] = unbound C_{max}	Not specified
R-value calculation method	R (R_3) = $1/(1 +d \times E_{max} \times 10 \times [I]/(EC_{50} + 10 \times [I]))$ [I] = unbound C_{max}, d = 1 R ≤ 0.8 for positive	Not specified	Not specified

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CYP mediated DDI-A comparison among FDA, EMA, and PMDA guidance and guidelines(V)

Item	FDA 2020	EMA 2013	PMDA 2018
Basic model	**Reversible inhibition:** $R_1 = 1+(I_{max,u}/K_{i,u})$ $R_{1,gut} = 1+(I_{max,u}/K_{i,u})$; only for CYP3A **Time-dependent inhibition:** $R_2 = (k_{obs}+k_{deg})/k_{deg}$ **Induction:** Fold change or correlation method $R_3 = 1/[1+d \times ((E_{max} \times 10 \times I_{max,u})/(EC_{50} + 10 \times I_{max,u}))]$	**Reversible inhibition:** $[I]/K_i \geq 0.02$; $[I] = C_{max,u}$ $[I]_{gut}/K_i \geq 10$; $[I]_{gut}$ = Dose/250mL; only for CYP3A **Time-dependent inhibition:** $R = (k_{obs}+k_{deg})/k_{deg}$ Induction: Fold change or correlation method.	**Reversible inhibition:** $[I]/K_i \geq 0.02$; $[I] = C_{max,u}$ $[I]_{gut}/K_i \geq 10$; $[I]_{gut}$ = Dose/250mL; only for CYP3A **Time-dependent inhibition:** $R = (k_{obs}+k_{deg})/k_{deg}$ Induction: Fold change or correlation method.
Static mechanistic models	If AUCR ($AUC_{\text{plus investigational drug}}/AUC_{\text{minus investigational drug}}$) is ≥ 1.25 (for inhibition) and ≤0.8 (for induction) a clinical DDI should be conducted using sensitive index substrate.	If AUCR is outside of 0.8 - 1.25, in vivo studies should be conducted to quantify the effect in vivo as well as, if needed, characterize the time course of the net effect.	If AUCR is outside of 0.8 - 1.25, in vivo studies should be conducted to quantify the effect in vivo as well as, if needed, characterize the time course of the net effect.

Conclusions

- New enzymes: FDA 2020 guidance recommends to consider two phase I enzymes, **AO and CES**, and a phase II enzyme, **SULTS**
- The major change with recent FDA and PMDA guidance, which aligns with the EMA, was to use **unbound concentrations** of investigational drug concentrations (**not total drug**) for the calculation of **DDI R cut-off values**
- All regulatory authorities recommend testing for **CYP1A2, 2B6 and 3A4 induction**, at least in the first instance
- The FDA, EMA and PMDA guidance(s) now **require major metabolites of parent drugs** (or those that contribute significantly to pharmacological activity or contain structural alerts for known DDI mechanisms) **to be assessed for DDI potential**

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