事　務　連　絡
平成 30 年 7 月 23 日

独立行政法人医薬品医療機器総合機構　御中

厚生労働省医薬・生活衛生局医薬品審査管理課

「医薬品開発と適正な情報提供のための薬物相互作用ガイドライン」に関する質疑応答集（Q&A）について

標記について、別添写しのとおり、別添写しのとおり、都道府県、保健所設置市及び特別区の衛生主管部（局）宛て連絡しましたので、お知らせします。

写

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平成 30 年 7 月 23 日

各（都道府県／保健所設置市／特別区）衛生主管部（局）　御中

厚生労働省医薬・生活衛生局医薬品審査管理課

「医薬品開発と適正な情報提供のための薬物相互作用ガイドライン」に関する質疑応答集（Q&A）について

医薬品の薬物相互作用の検討方法については、「医薬品開発と適正な情報提供のための薬物相互作用ガイドライン」（平成 30 年 7 月 23 日付け薬食審査発 0723 第４号厚生労働省医薬・生活衛生局医薬品審査管理課長通知）により示したところです。

今般、当該通知に関する質疑応答集を別添のとおり取りまとめましたので、ご承知の上、貴管下関係業者等に御周知方願います。

Q&A

Q1.

A1.

1.3

Q2. Contribution ratio; CR

A2. *In vitro* P450

in vitro fm fraction metabolized CR

P450

CR

fm CR CR

In vitro P450

in vivo

CL/F CL_{tot} CR

Q3. *In vitro*

A3. *In vitro* *in vivo*

S9 P450 UGT

1

S9

in vitro

In vitro

11.3 1-2

in vitro

in vitro *in vitro*

P450 P450

RAF Relative activity factor RAF

in vitro

Q4. TDI IC_{50}

A4. TDI IC_{50}
IC_{50} NADPH 30
IC_{50} IC_{50}
TDI NADPH
10
TDI
TDI
K_m 4
TDI
k_{inact} 50% K_I

k_{obs} k_{obs}
k_{inact} K_I k_{deg} P450
1)
k_{deg}
CYP3A k_{deg} 2)
TDI HIV

CYP3A TDI3) CYP2D6 TDI 4) TDI

k_{deg} k_{inact}
1 800mg
CYP3A 4 5)

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Q5.

A5. 3
80%

Q6.

A6.

[6] 1

in vitro EC_{50} E_{max}

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Q7.

A7. *In vitro* mRNA 50%

CYP2C9

[7]

in vitro

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Q8. AUC 10% AUC 10%

A8. AUC AUC

AUC

AUC

AUC AUC

AUC 10% AUC

10%

AUC

Q9. P450 P450 CYP2A6 2E1 2J2 4F2 *in vitro*

A9. CYP2A6 2E1 *in vitro*

[8-13]

CYP2A6	Coumarin 7-hydroxylation	Methoxsalen 8-Methoxypsoralen Tranylcypromine
CYP2E1	Chlorzoxazone 6-hydroxylation	Diethyldithiocarbamate Disulfiram Tranylcypromine Clomethiazole

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Q10. UGT *in vitro*

A10. UGT

UGT

UGT

UGT P450 UGT

UGT UGT1A1

1A3 1A4 1A6 1A9 2B7 2B15

UGT

UGT1A1 -

UGT1A4 UGT1A9 UGT2B7

14)

14) Miners JO, Mackenzie PI, Knights KM.: The prediction of drug-glucuronidation parameters in humans: UDP-glucuronosyltransferase enzymeselective substrate and inhibitor probes for reaction phenotyping and *in vitro–in vivo* extrapolation of drug clearance and drug-drug interaction potential. Drug Metab Rev. 2010;42:196-208.

Q11.

A11. IFN -2b P450

P450 15)

16)

15) Islam M, Frye RF, Richards TJ, Sbeitan I, Donnelly SS, Glue P, Agarwala SS, Kirkwood JM.: Differential effect of IFN -2b on the cytochrome P450 enzyme system: a potential basis of IFN toxicity and its modulation by other drugs. Clin Cancer Res. 2002;8:2480-7.
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Q12.

A12.

ABC (ATP binding cassette)
ATPase ATPase assay
[17]
P-gp BCRP
11.2 2-3 IC50 Caco-2
medium
Ki
[18] P-gp BCRP
Caco-2

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[19 20]

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Q13. MATE1 MATE2-K MATE1 MATE2-K

A13. MATE1 MATE2-K

MATE1 MATE2-K

BUN cystatin C

Q14. &

A14. &

Q15. MSPK

A15.

MSPK &

11.2 1-2 g) 3 f_m 1
AUCR
3

MSPK

$[I]_h$

$[I]_{u,inlet,\ max}$ $[I]_h = f_{u,b} \times ([I]_{max,b} + F_a \times F_g \times ka \times Dose/Q_H$ [21]

F_a F_g

ka Q_H 97 L/hr/70 kg [22]

$f_{u,b}$ $[I]_{max,b}$

99% $f_{u,b} = 0.01$

$[I]_g$ Q_{en} 18L/hr/70 kg [23] $[I]_g = F_a \times ka \times Dose/Q_{en}$ [24] ka

0.1/ ka F_g

B_h B_g

in vitro

in vitro EC_{50} E_{max}

in vivo d

d EC_{50} E_{max} AUCR

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Q16 PBPK

A16. PBPK

PBPK

Q17.

A17.

PBPK

Q18.

A18.

PBPK

Q19.

A19. CYP3A CYP2C9

[25 26]

CYP3A

OATP1B1 [27 28]

OATP1B1

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Q20.

A20. P450

C_{max} AUC

torsade de pointes

2 P450

CYP2C19

CYP3A CYP2C19

CYP2C19

CYP3A [29)]

CYP2C8 OATP1B1

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Q21.

A21. *in vitro*

C_{max} K_m

Q22.

A22. CYP2C19 CYP2D6

&

Q23. CYP3A

A23. CYP3A CYP3A

1 CYP3A

CYP3A

		CYP3A

CYP3A XXXX		CYP3A

2-1 CYP3A

CYP3A

		CYP3A

CYP3A XXXX		CYP3A
CYP3A		CYP3A

CYP3A		CYP3A

2-2 CYP3A CYP2D6

CYP3A CYP2D6

		CYP3A

CYP3A XXXX		CYP3A
CYP2D6		CYP2D6
CYP3A		CYP3A

Q24. CYP3A

A24. CYP2D6 CYP1A2

CYP3A

3 CYP2D6 CYP1A2

CYP2D6 CYP1A2

CYP2D6		CYP2D6
CYP1A2		CYP1A2 CYP1A2

4 CYP2B6 CYP2C8

CYP2B6 CYP2C8

		CYP2B6 CYP2C8

5 P-gp UGT1A1

UGT1A1 P-gp

P-gp		P-gp
		UGT1A1

Q25.

A25. *in vivo* Contribution Ratio CR
CYP CYP