



# Elsevier Life Science Solution

## PharmaPendium介绍以及案例分享

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爱思唯尔生命科学客户顾问



# 今天的内容

- ParmaPendium数据库的简介
  - PharmaPendium中的内容
  - PharmaPendium中的检索模块与基本应用
- ParmaPendium数据库的应用
  - 涉及药物的安全性、药效、DMPK数据获取的应用
    - 单一/一类药物数据的获取
    - 涉及特殊安全性研究（QT延长毒性）的相关报道的获取
  - 涉及新药申请方面的应用
    - 如何为非验证性“替代临床终点”提供证据支持
    - 如何为因“种族差异”导致的剂量差别寻找证据支持
  - Met代谢数据检索及DDI预测的应用
    - 抗肿瘤药物的代谢酶或转运体活性显著变化的信息检索
    - 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢
    - DDI预测应用

# PharmaPendium数据库涵盖的内容

- PharmaPendium是唯一提供上市药物，临床前与临床，药效，药物安全与药代动力学、药物代谢与转运酶，药物不良反应报告等数据的一站式平台；同时还收录此领域的权威期刊书籍内容，如Meyler副反应大全和Mosby用药参考等，助力药物筛选和研发进程。

FDA & EMA所有的approval package (FDA: 1938年- 今, EMA: 1995年— 今)

**2.29M+**  
FDA 审评文件

**200K+**  
EMA 审评文件

**9.45M+**  
FDA 药物不良反应  
报告

**673K+**  
FDA 咨询委员会会议  
档案

Extracted Data:

PK Module

MET Module

FDA AERS

Efficacy Module

DDI Risk

**4450**  
种药物的可检索  
信息

**1.6M+**  
药代动力学信息

**305K+**  
药物代谢与转运酶信  
息

**1.66M+**  
药物安全信息

**2.45M+**  
药效信息

**115K+**  
生物活性信息

# PharmaPendium深度提取FDA,EMA官方文档中的数据

PharmaPendium®

Browse Search My tools new

FDA Approval Package - Gefitinib > Medical/Clinical Review

原文分类整理

clinical review

获取原文后, 也可直接快速检索 '关键信息'

原文下载 Clinical Review 021399/S-000 Part 01

原文检索输入窗口

clinical review 26/198 Go

115%

CLINICAL REVIEW

Study type	Study pts.	Sample Size (N)	Design	1 <sup>o</sup> endpoint	2 <sup>o</sup> endpoint	Completion date
Adjuvant	Stage IB, II, III Resected	1160	Double-blind Placebo control	OS	DFS	10/07
Maintenance	Stage III Inoperable	840	Double-blind Placebo control	OS & PFS	-	5/06
First-line	Stage III/IV PS 2-3 LCS ≤20 Medical conditions	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06
Refractory	Stage III/IV PS 0-3	624	Double-blind BSC control	OS	PFS Symptoms	9/06
Refractory	Stage III/IV PS 0-2 LCS ≤20	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06

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# PharmaPendium深度提取FDA,EMA官方文档中的数据

PharmaPendium®

Browse Search My tools new

Quick Search

All These Sources

Drugs

Adverse Effects/Toxicity

Targets **靶点**

Indications **适应症**

Search >

Find adverse effect/toxicity data across preclinical, clinical, post-market reports and more

Pharmacokinetic Data

**数千条PK数据规范整理**

Metabolizing Enz. & Trans. Data

Drug Safety Data

FAERS Data new

Pharmacokinetic data search results

21381 records from PK Data: [Sofosbuvir; Velpatasvir (696) OR Interferon Alfacon-1 (8) OR Interferon Alfa-2b, Recombinant (205) OR Sofosbuvir; Velpatasvir; Voxilaprevir (553) OR Peginterferon Alfa-2b; Ribavirin (50) OR Ritonavir (0) OR Ledipasvir; Sofosbuvir (823) OR Telaprevir (1691) OR Simeprevir Sodium (1721) OR Elbasvir; Grazoprevir (569) OR Dasabuvir Sodium (27) OR Ribavirin (2818) OR Glecaprevir; Pibrentasvir (465) OR ...

Preclinical Data Clinical Data **All Data**

**直接查看**

ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value
1	Boceprevir	Human	healthy, Caucasian	400 mg	Oral	AUC(0-inf)(SCH 534129)	668.0 ng* <sup>h</sup> /mL
2	Boceprevir	Rat		3 mg/kg	Oral	Tmax(unchanged)	0.5 h
3	Boceprevir	Human	healthy, Caucasian	1200 mg	Oral	Tmax(unchanged)	2.4 h (1.0h - 4.0h)
4	Boceprevir	Cynomolgus monkey		25 mg/kg	Oral	RAC(unchanged)	1.99 dimensionless

Export date: 10-09-2018

Efficacy Data Search Results For: Drugs: [Gefitinib (684)] AND Phase: [III (684)]

Total results: 684

Sort order: Drug (Ascending); Indication Type (Ascending); Endpoint Type (Ascending);

**规范化数据导出**

Drug	Study Number	Phase/Combination	Study Design	Species	Sex	Route	Dose Regimen	Dose Frequency	Endpoint Type	Endpoint Subtype	Endpoint Tested	Value
Gefitinib	IPASS	III	Monotherapy	Human	Both	Oral	250 mg per day		Survival	Progression free survival	Treatment difference in progression-free survival	0.74
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate in EGFR mutation positive patients	47.3
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Complete response	Percentage of patients with complete response	0.8
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate in mutation unknown group of patients	29.2
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Disease control	Number of patients with disease control	482
Gefitinib	ISEL (D7913C00709)	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate in EGFR mutation negative patients	2.6
Gefitinib	ISEL (D7913C00709)	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	10.1
Gefitinib	ISEL	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate	1.6
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate in EGFR mutation positive patients	47.3
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Response	Number of EGFR mutation negative patients with objective response	20
Gefitinib	IPASS	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	43.0
Gefitinib	ISEL	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	2.6
Gefitinib	ISEL	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate	2.1
Gefitinib	Study 17	III	Combination	Human	Both	Oral	500 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	52.1
Gefitinib	Study 17	III	Combination	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	55.0
Gefitinib	INTEREST;ISEL;INVI	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Response	Number of patients with objective response in patients with EGFR FISH+ tumours	5
Gefitinib	Study 14	III	Combination	Human	Both	Oral	500 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	49.7
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Objective response	Objective response rate in mutation known group of patients	57.9
Gefitinib	IPASS (D791AC000)	III	Monotherapy	Human	Both	Oral	0		Clinical response	Stable disease	Number of patients with stable disease	286
Gefitinib	IPASS	III	Monotherapy	Human	Both	Oral	250 mg once daily	Once a day	Clinical response	Objective response	Objective response rate	43.3

# PharmaPendium中的基础检索----从适应症角度出发的检索

PharmaPendium®

Browse indications > Neoplasms benign, malignant and unspecified (incl cysts and polyps) > Hepatobiliary neoplasms malignant and unspecified > Hepatic neoplasms malignant > Hepatic cancer

hepatic cancer

输入对应词条即可：如，肝癌

适应症，靶点，药物的综合信息快速检索模式

Sources (All) [i]

Neoplasms benign, malignant and unspecified...  
Hepatobiliary neoplasms malignant and ...  
Hepatic neoplasms malignant  
Hepatic cancer

Drugs related to indication  
Showing 6 out of 8 items

Sources (All) [i] Export

Sources where Indication - Drug association is found

Drugs	FDA Label	EMA ANNEX	FDA Classic	Efficacy (FDA)	Efficacy (EMA)	DESI	MOSBY'S
Axitinib				Efficacy (FDA)			
Lenvatinib Mesylate					Efficacy (EMA)		
Nivolumab	FDA Label				Efficacy (EMA)		
Ramucirumab				Efficacy (FDA)			
Regorafenib		EMA ANNEX		Efficacy (FDA)	Efficacy (EMA)		
Romidepsin				Efficacy (FDA)			

肝癌获批的药物，已经在不同监管机构提交的数据

▼ Show all 8

Biology data: Hepatic cancer  
View Pharmacokinetic Data  
View Metabolizing Enz. & Trans. Data

# PharmaPendium中的基础检索---不同数据类型出发的模块化检索

PharmaPendium® Browse Search My tools

Pharmacokinetic data search Clinical & preclinical data

Drugs

- + Add drugs by drug class or drug name
- + Add drugs by primary target or primary target class
- + Add drugs by indication

Parameter ranges

- + Add parameter ranges

Species

- + Add species

Sources

- + Add sources

需要检索到数据细节时, 使用模块化检索: 如, 糖尿病类药物的PK综合信息

药物名或药物种类

靶点

适应症

参数种类

种属

来源

直接拿到具体数据

ID	Drug	Species	Study Group	Dose	Parameter	Parameter Value	SD
1	Glimepiride (14C-labelled)	Dog		0.01-10 ug/r	protein binding	99.0 %	
2	Glimepiride	Mammal (unspecified)		Unreported	In Vitro serum protein binding	<=99.0%	
3	Glimepiride (14C-labelled)	Human		0.01-10 ug/ml	In Vitro serum protein binding	99.4 %	
4	Glimepiride	Human		Unreported	In Vitro serum protein binding(M2 metabolite)	96.0 %	
5	Glimepiride (14C-labelled)	Human		Unreported	In Vitro serum protein binding	99.7% - 99.9%	
6	Glimepiride (14C-labelled)	Rabbit		0.01-10 ug/ml	In Vitro serum protein binding	99.2 %	
7	Glimepiride	Human		Unreported	In Vitro serum protein binding(alpha1-acid	94.0 %	

# PharmaPendium中的基础检索---FDA/EMA的PDF原文快速检索

PharmaPendium®

Browse Search My tools Peng Wu

Advanced search

也可以对原文的关键词信息进行快速组合检索：  
如，抗肿瘤的抗药抗体问题

Find results

... with all the words:  多个关键词直接输入

... within at least  words of one another

... with at least one of the words:  设定关键词间隔

... without the words:

Include synonyms

Drugs

抗肿瘤药物

+ Add drugs by drug class or drug name

+ Add drugs by primary target or primary target class

Sources

+ Add sources

Advanced Search Tips

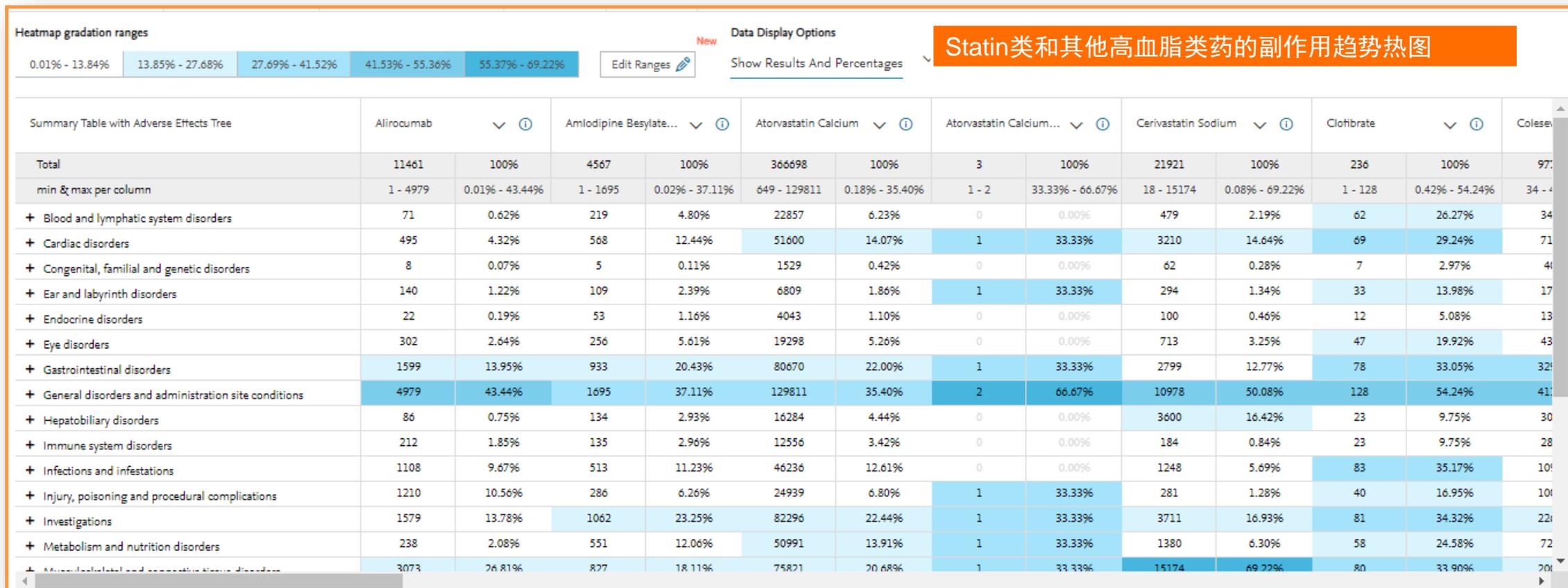
- Use the 1st field for proximity searching. Proximity terms (1st field) are searched using the proximity search. The proximity search does NOT search for synonyms. Wildcards (\* or ?) can be used here. The number at the end (distance) is how close in the document you want all the words to be. The default distance for this search is 200 words. Proximity Searches can also be done on the Quick Search bar using the syntax [term1] [distance] [term2].
- In the second field you can enter single words. All terms entered here will be searched and synonyms are ignored. Synonyms can be searched on entries in this field. Wildcards (\* or ?) can be used here. Quick Search syntax example: AND (term1 OR term2).
- In the third field you can enter single words. Synonyms can be searched. All terms entered here will be searched and synonyms are ignored. Synonyms can be searched on entries in this field. NOT search combined with search terms listed in the top 2 fields. Only documents NOT containing these words will be retrieved. Wildcards (\* or ?) can be used here. Quick Search syntax example: NOT (term1 OR term2).

ID	Document with context	Drug name	Source	Year
1	Review 210951/S-000 Part 02 PDF 536k ... <b>Antibody</b> Responses Conduct an assessment of binding and neutralizing <b>anti-drug antibody</b> (ADA) responses ... Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." • <b>Anti-Drug</b> ... pharmacokinetic trial with repeat doses of aCYP#X# inducer on the single dose pharm ... the magnitude of decreased <b>drug</b> exposure and to determine appropriate dosing recommendations. Design ...	Apalutamide	FDA approval packages	2017
2	Background Part 10 (Bone, Reproductive and Urologic Drugs Advisory Committee) PDF 390k ... ) Total Hip, mean % (SD) Femoral Neck, mean % (SD) ADA- <b>anti-drug antibody</b> ADA ADA binding Antibody ...) Effects of <b>anti-drug antibody</b> development on safety parameters: When evaluated based on antibody status ...		FDA Advisory Committee Documents	2019
3	Chemistry Review 125011/S-0000 PDF 1047k ... production and testing of <b>Anti-B1 Antibody</b> bulk <b>drug</b> substance (BDS) and packaged bulk drug substance (PBDS ... intended sources of product for commercial purposes, including <b>Anti-B1 Antibody</b> bulk <b>drug</b> substance (BDS ...), packaged bulk <b>drug</b> substance (PBDS) and ). MDS Nordion is responsible for inventory of <b>anti-B1 Antibody</b> ... <b>Antibody</b> PBDS and <b>drug</b> product (DP) and for labeling and packaging of <b>Anti-B1 Antibody</b> DP. The ...	Tositumomab	1 packages	
4	Background Part 10 (Arthritis Drugs Advisory Committee) PDF 2316k ... to disrupt <b>drug-anti-drug antibody</b> immune complexes, resulting in better <b>drug</b> tolerance. <b>Drug</b> ... added to the sample. If <b>anti-drug</b> antibodies are present in the sample, the <b>anti-drug antibody</b> will form ... factor) to capture the <b>anti-drug antibody-drug</b> conjugate complex. The amount of <b>anti-drug antibody</b> ... adalimumab comparator assay(s). The immunological cross-reactivity of <b>anti-drug antibody</b> results was ...	N/A	FDA Advisory Committee Documents	2016
5	Letter 022458/S-012 PDF 261k ... Approval supplemental new <b>drug</b> application clarifies the status of a patient that was <b>anti-drug antibody</b> ... Strategy 500 Arcola Rd, Collegeville, PA 19426 Dear Ms. Stewart: Please refer to your Supplemental New <b>Drug</b> ... ) of the Federal Food, <b>Drug</b> , and Cosmetic Act (FDCA) for Eleylso (taliglucerase alfa). This Prior ...	Taliglucerase Alfa	FDA approval packages	2016
6	Pharmacology Review 761071/S-000 Part 07 PDF 301k ... which may have led to false negative results despite acid dissociation of the <b>anti-drug antibody</b> /drug ... , even at prolonged sampling times, to interfere with <b>anti-drug antibody</b> detection. Based on this study ... treated animals for <b>anti-adalimumab antibody</b> detection exhibited high plasma concentrations of GP2017 ... observed. Similar amounts of <b>drug</b> accumulation (~2.5-fold) were observed over the treatment period. No <b>anti-</b>	Adalimumab	FDA approval packages	2018

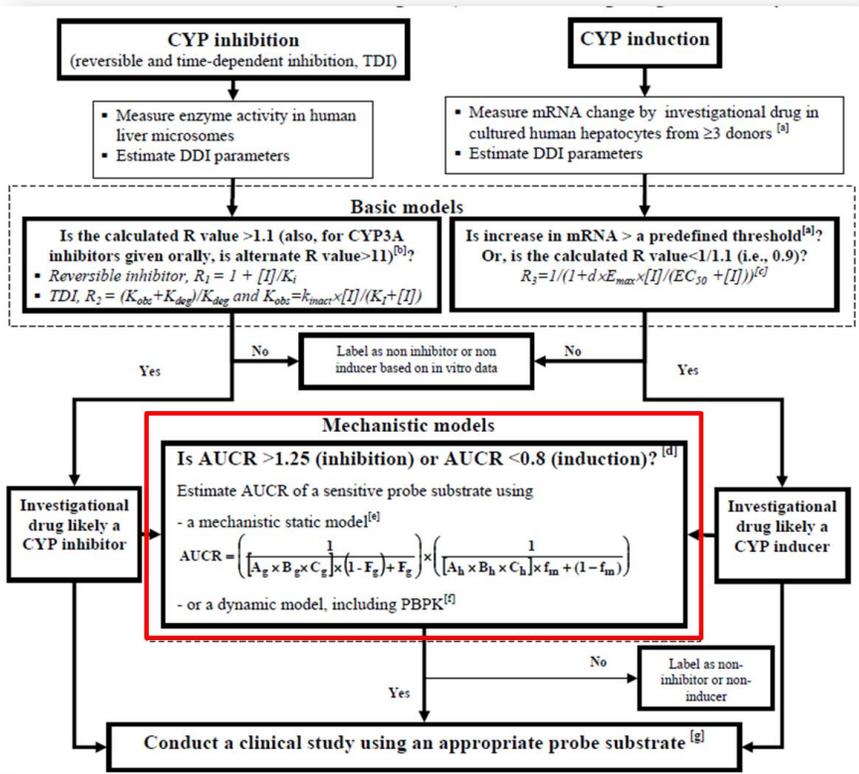
FDA审批文件

FDA评审委员会会议档案

# PharmaPendium中的基础应用---副作用分析



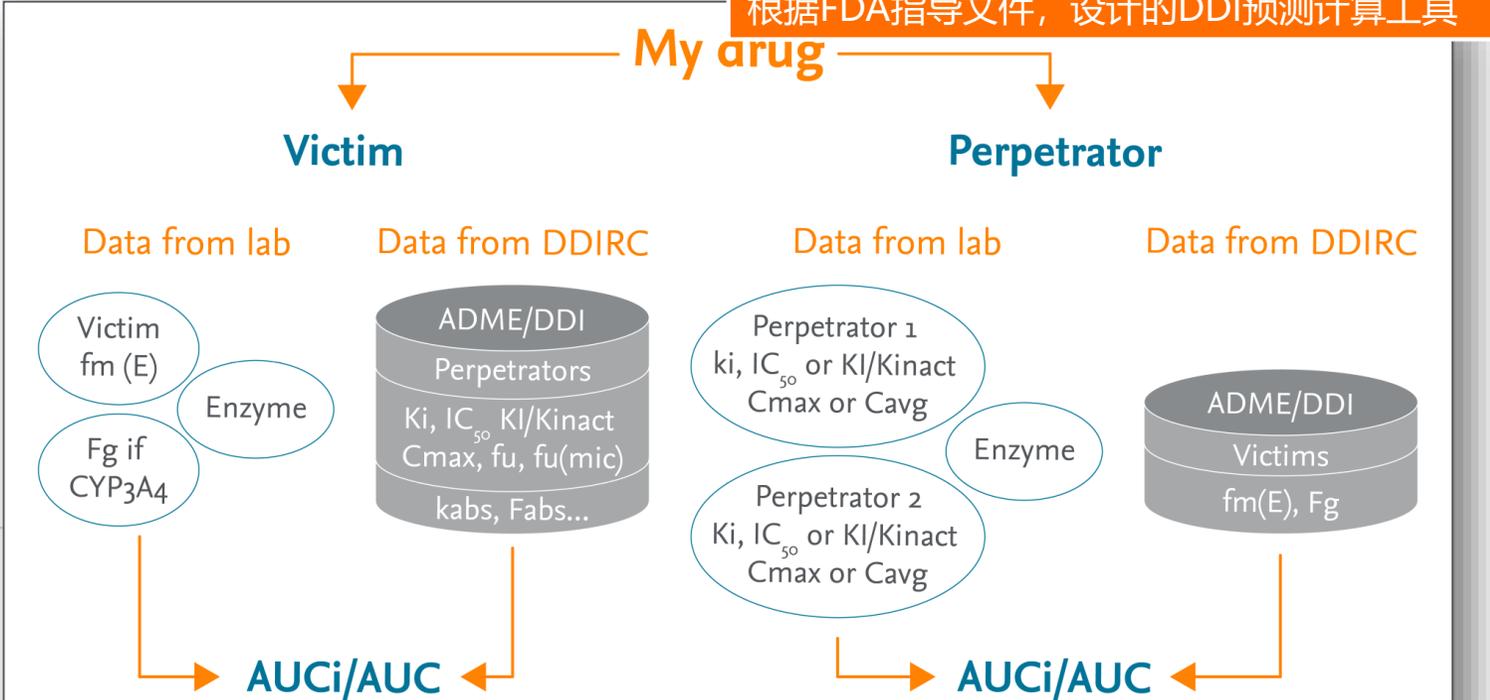
# PharmaPendium中的进阶模块--- DDI预测计算



Guidance for Industry Drug Interaction Studies  
 Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations  
 February 2012

“本指南反映了监管机构的观点，即在药物开发过程中，作为对药物安全性和有效性的充分评估的一部分，应确定研究性新药和其他药物之间的药代动力学相互作用。”

根据FDA指导文件，设计的DDI预测计算工具



# DDI预测计算结果—辅助实验方案制定

DDI Prediction 257 records from DDI Risk Calculator: Victim: Test

Results

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min.	Max.	Mean
1	(+)-Propoxyphene 91412 Analgesic; narcotic/opiate Dev.: + Drug Type: Approved	Multiple			4	1.061	1.554	1.308
2	(+)-Warfarin 162426 Antithrombotic Dev.: + Drug Type: Experimental/Investigation	0.007 g			1	1.075	1.075	1.075
3	(-)-Omeprazole 162827 Antilulcerative Proton pump inhibitor Dev.: - Drug Type: Approved	Multiple			88	1.022	1.078	1.051
4	(-)-Warfarin 161583 Antithrombotic Dev.: - Drug Type: Experimental/Investigation	0.007 g			5	1.033	1.142	1.094
5	AMG 487 628746 Dev.: - Drug Type: Unspecified	Multiple			3	2.82	18.223	6.42
6	Acamprosate 241873 Drug Type: Approved	Multiple			2646	1.012	1.271	1.1
7	Acetaminophen 99468 Analgesic; non narcotic	Multiple			72	4.048	4.134	4.088

**Bar chart information**

The bar chart displayed in the DDI table is a color coded graphical overview of the risk assessment.

Color codes represent AUCi/AUC ratio ranges corresponding to the FDA classification [1] of CYP inhibitor and inducer potency. The size of each colored segment in the bar represents the percentage of the total number of calculated AUC ratios (for a given victim/perpetrator couple) that falls into one of the following categories:

Category	AUC ratio range	Colour
Risk(Induction)	AUC ratio < 0.8	Blue
No risk	0.8 ≤ AUC ratio < 1.25	Green
Low risk	1.25 ≤ AUC ratio < 2	Yellow
Medium risk	2 ≤ AUC ratio < 5	Orange
High risk	5 ≤ AUC ratio	Red

[1] <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...>

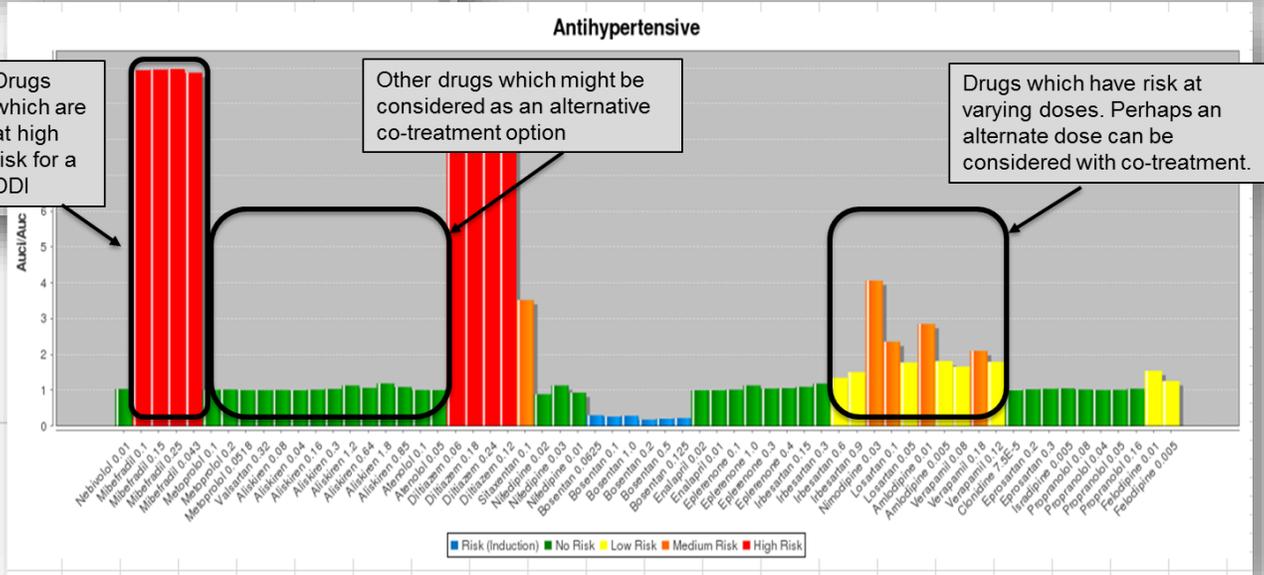
预测与上市药物DDI风险细节，包含剂量不同时的风险

## Dose effect

Dose	AUC Ratio	Count	Min	Max.	Mean	SD	Med.	5-95th Perc.
0.025 g		1	2.82	2.82	2.82	0.0	2.82	2.82-2.82
0.1 g		1	7.778	7.778	7.778	0.0	7.778	7.778-7.778
0.25 g		1	18.223	18.223	18.223	0.0	18.223	18.223-18.223

**Example:** We are developing a drug to treat diabetes. This patient population is frequently prescribed anti-hypertensives – how can I see the risk of potential drug-drug interactions with anti-hypertensives?

总览各类型要与在研药物可能存在的风险



# Novartis: 利用PharmPendium中已上市药物的信息预测在研药物临床安全

## Accessing Marketed Drug Information from PharmaPendium to Inform PreClinical Safety

Duncan Armstrong  
Preclinical Secondary Pharmacology, Novartis

Pooja Jain  
Product Manager, PharmaPendium, Elsevier



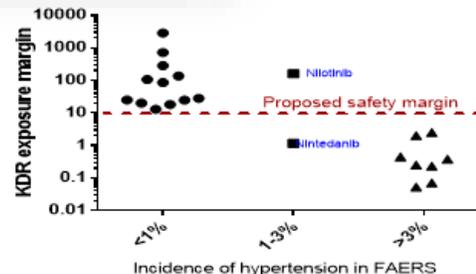
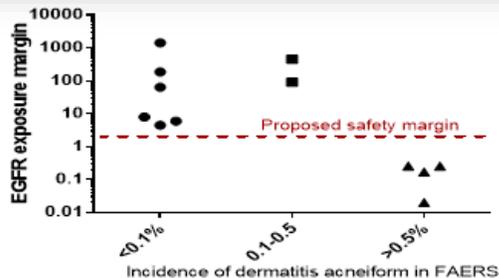
NOVARTIS

- List of marketed drugs with known ADR (QT prolongation, TdP)
- Effective Therapeutic Plasma Concentration  $ETPC_{(unbound)}$  identified in the literature
- Activity in in vitro assay of hERG block measured

$$\text{Safety Margin} = \frac{\text{In vitro IC50}}{ETPC_{(unbound)}}$$

IMPACT: simple, rapid, inexpensive in vitro hERG assay routinely implemented in early discovery. Molecules with poor safety margin are deprioritized

Redfern et al (2003) Cardiovascular Research 58(1):32-45. Figure 3



NOVARTIS



# 今天的内容

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    - 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢
    - DDI



## 药物安全性，药效，DMPK数据的获取

**Case 1: Paclitaxel 临床前信息检索**

**Case 2: 他汀类药物的临床前毒理药理信息**

**Case 3: QT延长趋势研究**



# Case 1: 紫杉醇 (Paclitaxel) 临床前信息检索

**快速的基于药物的检索**

PharmaPendium®

paclitaxel

Antineoplastics  
Antineoplastics, antimitotics  
Paclitaxel

Paclitaxel

Brands: Abraxane, Anzatax, Apeales, Asotax, Biotax, Bristaxol, Britaxol, Formoxol, Genexol, Ifaxol, Intaxel, Medixel, Mitotax, Onxol, Opaxio, Pacitaxel, Pacxel, Padexol, Parexel, Paxene, Paxus, Praxel, Taxocris, Taxol, Taycovit

Documents: [View FDA approval packages](#)  
[View EMA approval documents](#)  
[View Mosby's Drug Consult™: Paclitaxel](#)

Meyler's Side Effects: [View Meyler's: CHAPTER.45 Cytostatic and Immunosuppressant Drugs > Paclitaxel](#)  
[View Meyler's: CHAPTER.45 Cytostatic and Immunosuppressant Drugs > Cytostatic and Immunosuppressant Drugs](#)

Biology data: [View Pharmacokinetic Data](#)  
[View Metabolizing Enz. & Trans. Data](#)  
[View Drug Safety Data](#)  
[View FAERS Data](#)  
[View Efficacy Data](#)  
[View Activity Data](#)

Classes: Antineoplastics, antimitotics

Indications  
Showing 6 out of 21 items

Sources (All) | Export

**FDA/EMA 审批文档, 点击可以查看原文**

**整理后的综合数据, 包含临床前, 临床**

ELSEVIER

# 对原始文献的便捷查询

**PharmaPendium®**

FDA Approval Package

Search this FDA Package

- > Administrative documents
- > Approval Letter
- > Approval Package
- > Bioequivalence Review
- > Chemistry Review
- > Clinical Pharmacology and Biopharmaceutics Re...
- > Correspondence
- > Environmental Review
- > Label
- > Letter
- > Medical Officer Review
- > Medical/Clinical Review
- > Microbiology Review
- > Pharmacology Review
- > Printed Labeling
- > Statistical Review

**分门类整理FDA原始档案**

FDA Approval Package

Search this FDA Package

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Label 021660/S-045

**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE.

**ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)**  
(albumin-bound)  
Initial U.S. Approval: 2005

**WARNING: NEUTROPENIA**  
See full prescribing information for complete boxed warning.

- Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. (4)
- It is recommended that frequent peripheral blood cell counts be performed to monitor the occurrence of bone marrow suppression. (4, 5.1, 6.1, 6.2, 6.3)

**DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

**RECENT MAJOR CHANGES**

- Warnings and Precautions, Hypersensitivity (5.5) 08/2018
- Warnings and Precautions, Embryo-Fetal Toxicity (5.8) 08/2018

**INDICATIONS AND USAGE**

ABRAXANE is a microtubule inhibitor indicated for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. (1.1)
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemtuzumab. (1.3)

**DOSAGE FORMS AND STRENGTHS**

For injectable suspension: lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution. (3)

**CONTRAINDICATIONS**

- Neutrophil counts of < 1,500 cells/mm<sup>3</sup>. (4)
- Severe hypersensitivity reaction to ABRAXANE. (4)

**WARNINGS AND PRECAUTIONS**

- ABRAXANE causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed. (5.1)
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemtuzumab; interrupt ABRAXANE and gemtuzumab until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm<sup>3</sup>, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemtuzumab; permanently discontinue treatment with ABRAXANE and gemtuzumab. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.6)
- ABRAXANE contains a human albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- ABRAXANE can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)

**ADVERSE REACTIONS**

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are: back pain, neutropenia, sensory neuropathy, abnormal ECG, fatigue, asthenia, myalgia, arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)

**并对后续的研究作及时的更新**

- 2018-08-17 PDF(1120k)  
Label 021660/S-045
- 2015-07-22 PDF(492k)  
Label 021660/S-041
- 2015-03-05 PDF(1010k)  
Label 020262/S-051
- 2015-01-08 PDF(533k)  
Label 021660/S-040
- 2013-10-31 PDF(1120k)  
Label 021660/S-038
- 2013-09-06 PDF(1032k)  
Label 021660/S-037
- 2013-06-11 PDF(837k)  
Label 021660/S-036
- 2013-03-12 PDF(717k)  
Label 076131/S-022
- 2012-10-01 PDF(433k)  
Label 021660/S-031
- 2012-09-01 PDF(647k)  
Label 021660/S-034, S-035

1 of 25

# 原始文档--临床前信息整理，便于分析处理

PharmaPendium®

Pharmacokinetic data search results

2496 records from PK Data: [Paclitaxel (2496)]

Filters

Refine search:

- Apply
- Clear all

Parameter ranges

Drugs

Routes of Administration

Sources

Study Group

Radiolabelled

Metabolites/Enantiomers

Tissue specific

Concomitant

Years

Preclinical Data

Original document information, PK data整理如下, 包含临床前, 临床

Parameter ranges

- Absorption (180)
- Binding (11)
- Biotransformation (7)
- Distribution (189)
- Elimination (151)

Sources

- FDA approval packages (136)
- EMA approval documents (114)
- PharmaPendium Published PK ..

Species

- Vertebrates (538)
  - Mammals (538)
    - Carnivora (34)
      - Dog (34)
    - Lagomorph (1)
      - Rabbit (1)
    - Rodent (503)
      - Mouse (211)
      - Rat (292)

Routes of Administration

- In Vitro (11)
- Intraarterial (1)
- Intravenous (475)
- Oral (47)

查看原文

多种筛选器快速处理数据

ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value	SD	t	Concomitants
1						Cmax(median)	3916.0 ng/mL (496.0ng/mL - 8313.0ng/mL)			
2					Oral	Cmax(3'-p-Hydroxy paclitaxel)	0.03 uM	0.02		Clemastine Fumarate
3					Intravenous	T1/2abs	0.72 h			Dexamethasone
4				60 mg/m2	Oral	AUC(0-inf)(6,3'-p-Dihydroxy paclitaxel)	0.62 uM*h	0.59		Ranitidine
5	Paclitaxel	Human		135 mg/m2	Intravenous	Cmax	3841.0			
6	Paclitaxel	Human	with cancer; neuro grade.	75-560 mg		AUC(median)	14.1 ng*h/mL (8.8ng*h/mL - 24.8ng*h/mL)			
7			ovarian			CLt	23.8 L/h/m2			
8			advanced tumor			Tmax(median)	0.36 h (0.0h - 0.5h)			
9			advanced tumor			AUC(0-inf)(whole blood)	32525.0 ng*h/mL			
10			cancer	170 mg/m2	Intravenous	Vss	8.5 L/m2 (4.9L/m2 - 11.8L/m2)			
11				175 mg/m2	Intravenous	AUC(0-inf)	13.5 ug*h/mL	3.22		

# 更便捷的追踪原文

Preclinical Data			Clinical Data			All Data		
ID	Drug	↗↑	Parameter Value	SD	t	Concomitants	Source	Year
1	Paclitaxel (3H-labelled)		5.6 nCi/g		24 h		EMA approval document: Assessment Report (Page:12) View Full Study PDF 662k	
2	Paclitaxel		20.27 ug*h/mL		24 h		PharmaPendium Published PK: European Journal of Pharmaceutical Sciences 2016; 83:79 Locate Article View Full Study	2016
3	Paclitaxel (3H-labelled)		692.0 mL/kg					
4	Paclitaxel (3H-labelled)		3.7 ug-eq*h/mL					
5	Paclitaxel (3H-labelled)		6.1 ug-eq*h/mL					
6	Paclitaxel		36.28 ug*h/mL					

**PharmaPendium®**

EMA Approval Package

Search this EMA Package

- PDF(662k) Assessment Report EMA/47053/...
- 2018-07-25 PDF(168k) Assessment Report EMA/COMP1...
- 2015-01-22 PDF(3352k) Assessment Report EMA/76768/2...
- 2013-11-21 PDF(2530k) Assessment Report EMA/CHMP/6...

- Information on Procedure
- Medicine Overview
- Other information from EMA
- Positive Opinion Summary
- Press Release
- Procedural Steps
- Public Assessment Report
- Q&A
- Risk Management Plan Summary
- Scientific Discussion

EMA Approval Package > Paclitaxel > Assessment Report > Assessment Report EMA/47053/2008; EMEA/H/C/778

Assessment Report EMA/47053/2008; EMEA/H/C/778

75%

Table 3: Studies conducted to assess pharmacokinetic properties of paclitaxel in animals

Type of study	Study ID	Species	GLP compliant
Absorption, distribution, excretion	P0796003	Rat	Yes
Absorption, distribution, excretion	P0966001	Rat	Yes
Absorption	P0297003	Rat	Yes
Absorption	A.FIP-002	Rabbit	Yes
Distribution	A.590.1	Mouse	No
Distribution	A.590.1.2	Mouse	No
Distribution/metabolism/excretion	P0202002	Rat	Yes
Other	P0203014	Rat	Yes
Other	NF001106	Rat	Yes

Two types of analysis were employed for the determination of paclitaxel in the pharmacokinetic studies, liquid scintillation counting (LSC) of tritium (<sup>3</sup>H) labelled Abraxane or solvent-based paclitaxel and a validated liquid chromatography with atmospheric pressure ionisation tandem mass spectrometry detection (LC-AP/MS/MS). LSC was calibrated to report counts above background noise. The lower limit of quantification for the LC/MS method is 5 ng/mL, and the range of reliable responses is 5-1000 ng/mL.

- Absorption-Bioavailability

Studies on absorption for Abraxane were not provided since it is developed for iv infusion. Conventional studies on pharmacokinetic (PK) parameters after iv administration have been examined in rats, and after intra-arterial injection in rabbits.

Three studies in male rats were performed to compare PK parameters of <sup>3</sup>H-paclitaxel formulated in Abraxane and solvent-based paclitaxel. Blood samples were collected from 2 minutes to 24 hours after dosing and control for total radioactivity. Pharmacokinetic results obtained in blood are presented in Table 4.

Treatment	Dose (mg/kg)	n	AUC <sub>0-∞</sub> (ng·h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	T <sub>1/2β</sub> (h)	Study
<sup>3</sup> H-Abraxane	3.1	5	11.5	7.19	0.03	22.3	P0297003
	26.4	5	43.5	29.5	0.03	16.0	P0297003
	116.7	5	248.9	283.3	0.03	8.68	P0297003
Solvent-based paclitaxel	3.1	5	355.3	414.2	0.01	9.34	P0297003

Table 5: PK parameters in blood, plasma and tumour levels of <sup>3</sup>H-Abraxane in mice

Treatment	iv dose (mg/kg)	Sample (n)	AUC <sub>0-∞</sub> (ng·h/mL)	Clearance (mL/h/kg)	V <sub>d</sub> (mL/kg)	T <sub>1/2β</sub> (h)
<sup>3</sup> H-Abraxane	21.7	Blood	939	254	6239	17.1
		Plasma	1181	397	2190	16.1
		Tumour	5869	NA	NA	48.2
<sup>3</sup> H-solvent based paclitaxel	19.5	Blood	871	382	1409	4.0
		Plasma	1438	231	692	3.3
		Tumour	3716	NA	NA	28.1

The distribution of <sup>3</sup>H-Abraxane (20 mg/kg) to different major organs was investigated in a 24-hour study in female (6/group) mice bearing subcutaneous, implanted MX-1 human mammary tumours after iv injection (study A590.1.2). Results are shown in Table 5.

Table 6: Blood, plasma, tumour, and tissue levels of radioactivity in mice given <sup>3</sup>H-Abraxane

Time	Mean Values (nCi/g)									
	Heart	Kidney	Lungs	Liver	Muscle	Spleen	Stomach	Tumour	Blood	Plasma
5 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	28	157	186
15 min	355	568	334	2391	116	299	6.7	89	85	117
30 min	N.D.	N.D.	3.40	N.D.	N.D.	N.D.	N.D.	1160	99	70
60 min	121	206	136	1366	14	105	5.7	132	39	39
3 hrs	56	114	79	650	109	121	7.6	138	17	16
8 hrs	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	28	6.3	7.9
24 hrs	5.8	0.9	8.3	24	4.5	3.4	5.6	60	4.9	6.5

nCi: Nanocurie N.D.: Not Determined

The distribution of Abraxane was investigated also in healthy rats. Study P02020025 included 5 male and 5 female rats per group following a single iv injection of <sup>3</sup>H-Abraxane (5 mg/kg) and compared to <sup>3</sup>H-solvent based paclitaxel (5 mg/kg). For most tissues the exposure levels were slightly higher in animals treated with Abraxane than with solvent-based paclitaxel. In lungs, there was a 3.5-fold higher concentration of solvent-based paclitaxel compared to Abraxane. Males had slightly higher exposure of Abraxane in all measured tissues except for fat. For solvent-based paclitaxel the males had slightly

所有原文都支持“text searching”便于快速定位细节

pharmapendium.com/rend/184/browse/content/.../pdfViewerContent.html

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# 原文界面 ‘关键词’ 直接检索

EMA Approval Package > Paclitaxel > Assessment Report > Assessment Report EMEA/47053/2008; EMEA/H/C/778

## Assessment Report EMEA/47053/2008; EMEA/H/C/778

adverse

adverse

adverse

adverse

17

Go

15%

manifestations confined to the axillary lymph nodes, overlying skin, the underlying chest wall or to more distant disease. Overt metastases to other organs are referred to as metastatic disease (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004).

Metastatic breast cancer (MBC) remains an incurable disease with a median survival of about 2 years; treatment is therefore essentially palliative (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004). The types of treatment used in MBC can be categorised as endocrine, chemotherapy and biological therapy. Generally, initial treatment in patients with nonaggressive, hormone-sensitive tumours is with endocrine therapy. Tamoxifen and aromatase inhibitors are the most widely used endocrine therapy. In patients with hormone-insensitive or aggressive tumours, chemotherapy is the usual initial treatment (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004). A anthracycline-containing regimens include 5-fluorouracil, doxorubicin and cyclophosphamide (FA C) and 5-fluorouracil, epirubicin and cyclophosphamide (FEC), and the most common non-anthracycline containing regimen is cyclophosphamide, methotrexate and 5-fluorouracil (CMF). With the growing use of anthracycline-containing therapy as adjuvant therapy, the taxanes (paclitaxel and docetaxel) have become established as the standard of care in patients with anthracyclines-resistant MBC (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004; Gralow 2005). Taxanes are also used in patients with MBC with no or minimal prior anthracycline exposure. Following failure of anthracyclines and taxanes, various agents are available, including capecitabine and vinorelbine. As biological therapy he monoclonal antibody, trastuzumab (Herceptin) is available for the treatment of ErbB2 overexpressing breast cancer.

The antineoplastic mechanism of action of paclitaxel as an antimicrotubule agent is well characterized (Schiff, Fant et al. 1979; Schiff and Horwitz 1980). Paclitaxel in a solvent-based cremophor EL formulation has been authorized and marketed in Europe since 1993 (Taxol). As a single agent, solvent-based paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy. In combination solvent-based paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either with an anthracycline in patients for whom anthracycline therapy is suitable, or with trastuzumab, in patients who over-express HER-2 at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.

**About the product:**

Abraxane is a cremophor-free colloidal suspension of paclitaxel and human serum albumin. Abraxane is a new formulation developed to overcome the water insolubility of the active component paclitaxel and prevent hypersensitivity reactions associated with solvent-containing formulations. Abraxane is presented lyophilized and contains 800 mg albumin per 100 mg paclitaxel prior to reconstitution with 0.9% saline. The size of the paclitaxel nanoparticles is approx. 130 nm.

The applicant has submitted an application for a full marketing authorization under Article 8(3) of Directive 2001/83/EC (as amended). The claimed indications and posologies were metastatic breast carcinoma (260 mg/m<sup>2</sup> administered intravenously over 30 minutes every 3 weeks) and adjuvant treatment of node-positive breast carcinoma following anthracycline and cyclophosphamide therapy (260 mg/m<sup>2</sup> administered intravenously over 30 minutes every 3 weeks for 4 courses). Clinical data to

paclitaxel per ml. Paclitaxel is present in the form of albumin-bound nanoparticles with a mean size of approximately 130 nm.

Other ingredients include human albumin solution, water for injections and nitrogen. Only human albumin is left in the finished product.

The product is packaged type I glass vials closed with a bromobutyl rubber stopper and an aluminium crimp seal. A cardboard box is used to protect the product from light.

**Active Substance**

Paclitaxel is a known active substance described in the Ph. Eur. Paclitaxel is : 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. It is a white, practically insoluble in water (less than 0.5 mg/ml), soluble in dichloromethane. Paclitaxel has 11 stereogenic centres and m However only one crystal form of paclitaxel is found in the active of the finished product

The chemical structure of paclitaxel has been confirmed using IR, <sup>1</sup>H- and <sup>13</sup>C-NMR, UV and mass spectrometry. The solid by means of thermal analysis (differential scanning calorimetry).

- **Manufacture**  
Paclitaxel is manufactured by extraction from the Taxus liquid/liquid extractions, chromatographic column purified granulation and drying. Detailed information about the controls of the active substance has been provided using the A The starting material has been adequately characterized and Pesticides Residues. Appropriate specifications have been at processing aids and intermediates. All relevant impurities he degradation studies have shown the major degradation products) have been characterized. The levels of the imp toxicological studies and appropriate specifications have been
- **Specification**  
The active substance specification includes tests for app specific optical rotation, related substances (HPLC), assay (H heavy metals, residual solvents, microbial purity and endotox Batch analysis data from 13 production scale batches and provided. In all cases the product complied with the predefine
- **Stability**  
Stability studies have been performed in accordance with the production scale batches have been stored for 36 months at 25 40 °C/75 % RH. The packaging materials used in the stability for marketing.

- Discontinuation due to **adverse** events

The proportion of patients on Abraxane that discontinued prematurely from study CA012-0 due to treatment-related **adverse** events was greater than with solvent-based paclitaxel (7% vs. 4%, respectively, not statistically significant). Sensory neuropathy mostly accounted for this difference. In 13 cases with sensory neuropathy related to Abraxane requiring dose reduction, 10 eventually became grade 3 events and three became grade 2 events.

- Post marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Abraxane. In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesiae have been reported as part of the continuing surveillance of Abraxane. Because these events have been reported voluntarily during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

- Discussion on clinical safety

In the randomized Phase III clinical study CA012-0 the degree of neutropenia (all or only Grade 4) was greater with solvent-based paclitaxel than with Abraxane, even though the dose of paclitaxel was 50% higher for Abraxane. The reduced myelosuppression for Abraxane is also consistent with the more rapid clearance of paclitaxel from the plasma for this formulation compared to solvent-based paclitaxel (Study CA008 and ((Sparreboom, Huizing et al. 1995)). The relationship between the PK variables of Abraxane and ANC Nadir values was evaluated using a regression model in which log-transformed ANC Nadir values were used to account for the non-linear (e.g. sigmoid) relationship between absolute neutrophil count (ANC Nadir) and PK variable. There is a significant relationship between absolute ANC Nadir value and the PK parameters of AUC<sub>inf</sub> and the Duration of Time that paclitaxel concentration remain at or above threshold concentrations of either 84 ng/ml or 42 ng/ml (p-values are <0.001, 0.031, and 0.017, respectively).

There is also a significant relationship between Percentage Decrease in ANC Nadir from Baseline and the PK parameters of AUC<sub>inf</sub> and the Duration of Time that paclitaxel concentration remains at or above a threshold concentration of 42 ng/ml (p-values are 0.004 and 0.030, respectively). For solvent-based paclitaxel, on the contrary, AUCs would not correlate with ANC nadirs, because it has a delayed tissue distribution due to retention in cremophor micelles and results in higher AUC values. However, since the effects of Cremophor on solvent-based paclitaxel PK are primarily in the 'early' distribution phase, as demonstrated by the similar terminal phases for Abraxane and solvent-based paclitaxel, the

## Case 2: 他汀类药物的临床前毒理药理信息

PharmaPendium®

Browse drugs > Antihyperlipidemics

Antihyperlipidemics

Drugs:

- Acipimox
- Aluminum Nicotinate
- Amlodipine Besylate; Atorvastatin Calcium
- Ascorbic Acid; Calcium Pantothenate; Cyanocobalamin; Nicotinic Acid; Pyridoxine Hydrochloride; Riboflavin; Thiamine Mononitrate
- Atorvastatin Calcium
- Atorvastatin Calcium; Ezetimibe
- Beclobrate
- Bervastatin
- Bezafibrate
- Biclofibrate
- Binifibrate
- Cerivastatin Sodium
- Cholestyramine
- Choline Fenofibrate
- Ciprofibrate
- Clinofibrate
- Clofibrate
- Colesevelam Hydrochloride
- Colestipol Hydrochloride
- Crivastatin
- Cytellin
- Dalvastatin
- Dextrothyroxine Sodium
- Dulofibrate
- Etofibrate
- Ezetimibe
- Ezetimibe; Simvastatin
- Fenirofibrate
- Fenofibrate
- Fenofibrate; Metformin Hydrochloride
- Fenofibrate; Pravastatin Sodium
- Fenofibrate; Simvastatin
- Fenofibric Acid
- Fluvastatin Sodium
- Gemfibrozil
- Glenvastatin
- Icosapent Ethyl
- Lifibrate

一类型药物的数据综合比较，通过药物分类进行信息检索

- PP主要通过三种方式进行‘一类药物’检索：
  - 药物分类，靶点，适应症
- Statins在PP并不是一类型药物的分类
  - 通过‘Antihyperlipidemics’可以检索上市的降脂类药物
  - 通过‘靶点’检索statins类药物
  - 通过‘适应症’检索同类型药物

# 通过靶点检索对应药物

通过作用机制的靶点，可以快速索引到对应上市后药物

The screenshot shows the PharmaPendium interface. On the left, a 'Browse targets' sidebar is highlighted with an orange box, showing a tree structure: 'By SuperFamily' > 'Enzymes' > 'Oxidoreductases' > 'Hydroxymethylglutary...'. Below this, another orange box contains the text: '他汀类药物都具有相同的靶点，通过靶点快速获得这类药物的数据'. The main content area shows a breadcrumb path: 'Browse targets > By SuperFamily > Enzymes > Oxidoreductases > Hydroxymethylglutaryl-CoA Reductase'. Below this is a table of drugs with columns for FDA, EMEA, MEYLER, MOSBY, and XPHARM. The table lists several statins: Atorvastatin Calcium, Bervastatin, Cerivastatin Sodium, Crilvastatin, Cyclandelate, and Dalvastatin. Below the table, a section titled '快速获取各类综合信息' (Quickly get various comprehensive information) is highlighted with an orange box, listing links for 'Biology data: for drugs where this is the primary target', including 'View Pharmacokinetic Data', 'View Metabolizing Enz. & Trans. Data', 'View Drug Safety Data', 'View FAERS Data', 'View Efficacy Data', and 'View All Activity Data (Primary/Non-Primary) For: Hydroxymethylglutaryl-CoA Reductase'. At the bottom, there is a section for 'Adverse Effects / Toxicity (for drugs that interact with this target)\*' and an 'Export' button. The URL at the bottom left is 'https://www.pharmapendium.com/browse/drugs/Atorvastatin Calcium'.

Drugs	FDA	EMEA	MEYLER	MOSBY	XPHARM
Atorvastatin Calcium	FDA			MOSBY	XPHARM
Bervastatin			MEYLER		
Cerivastatin Sodium	FDA			MOSBY	XPHARM
Crilvastatin			MEYLER		
Cyclandelate			MEYLER		
Dalvastatin			MEYLER		

# Statin类药物数据比较-药效

Efficacy data search results **药效信息** Show/hide columns > Show drugs in... > Save Export

24829 records from Efficacy data: [Cerivastatin Sodium (1770) OR atorvastatin Calcium (6372) OR Pitavastatin (92) OR Fluvastatin Sodium (1313) OR Pitavastatin Calcium (1916) OR Simvastatin (3485) OR Pravastatin Sodium (3542) OR Rosuvastatin Calcium (3414) OR Lovastatin (2925)]

Preclinical Data Clinical Data

ID	Drug	Study Number	Phase	Mono/Combination	Study Design	Species	Sex	Age	Indication Type
1	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy	Prospective, randomized, open-label, blinded endpoint (PROBE) trial	Human	Both	Adult-aged	Cardiovascular event proph
2	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy	Prospective, randomized, open-label, blinded endpoint (PROBE) trial	Human	Both	Adult-aged	Cardiovascular event proph
3	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy	Prospective, randomized, open-label, blinded endpoint (PROBE) trial	Human	Both	Adult-aged	Cardiovascular event proph
4	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy					
5	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy					
6	Atorvastatin Calcium	TNT	Not specified	Monotherapy					
7	Atorvastatin Calcium	IDEAL	Not specified	Monotherapy					

Export date: 22-04-2019  
Efficacy Data Search Results For: Drugs: [Cerivastatin Sodium (1770) OR Atorvastatin Calcium (6372) OR Pitavastatin (92) OR Fluvastatin Sodium (1313) OR Pitavastatin Calcium (1916) OR Simvastatin (3485) OR Pravastatin Sodium (3542) OR Rosuvastatin Calcium (3414) OR Lovastatin (2925)]  
Total results: 24829  
Sort order: Drug (Ascending); Indication Type (Ascending); Endpoint Type (Ascending);

Drug	Study Number	Phase	Mono/Combination	Study Design	Species	Sex	Age	Indication Type	Indication	Route	Dose Regimen	Dose Frequency
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Open-label crossover study	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 or 80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	0 mg	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	40 mg	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Open-label crossover study	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	0 mg	
Atorvastatin Calcium	Study 2	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Study 1	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Combination	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia	Oral	0 mg/day; simvastatin 20 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	0	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Hyperlipidemia	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	0.0	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	24 controlled trials	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	0 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Hyperlipidemia	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	20 mg	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Double-blind, placebo-controlled study follow-up	Human	Both	Child-adolescent	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg QD for the first 4 weeks at	Once a day
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	10 mg daily	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Open-label crossover study	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	0	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	40 mg/day	
Atorvastatin Calcium	Study 3	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	0	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	10 mg	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Open-label crossover study	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 or 80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Combination	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia	Oral	0 mg/day; simvastatin 20 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	0 mg daily + Simvastatin 10 mg	
Atorvastatin Calcium	Study 3	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	0	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	Hyperlipidemia	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	10 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	24 controlled trials	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an adjuvant	Oral	80 mg/day	
Atorvastatin Calcium	Not specified	Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia	Oral	10 mg	

Efficacy Data

以上数据即可导出规整的Excel表格便于分析

ELSEVIER

# 通过“适应症”获取相关上市药物信息

‘hyperlipidemia’（高血脂）相关的药物，可以对比‘他汀’类药物与其他同类型药物，辅助研究

The screenshot shows the PharmaPendium website interface. The main content area displays 'Hyperlipidemia' with a list of drugs related to this indication. A sidebar on the left shows a navigation tree for 'hyperlipidemia' with 'Hyperlipidemia' highlighted. The table below lists drugs and the sources where the indication-drug association is found.

Drugs	Sources where Indication - Drug association is found						
	FDA Label	EMA ANNEX	FDA Classic	Efficacy (FDA)	Efficacy (EMA)	DESI	MOSBY'S
Alirocumab				Efficacy (FDA)			
Aluminum Nicotinate						DESI	
Amlodipine Besylate; Atorvastatin Calcium				Efficacy (FDA)			MOSBY'S
Atorvastatin Calcium	FDA Label			Efficacy (FDA)			MOSBY'S
Atorvastatin Calcium; Ezetimibe	FDA Label						
Cerivastatin Sodium							MOSBY'S
Clofibrate							MOSBY'S
Colesevelam Hydrochloride				Efficacy (FDA)	Efficacy (EMA)		
Colestipol Hydrochloride							MOSBY'S
Evolocumab	FDA Label			Efficacy (FDA)	Efficacy (EMA)		

# 整理所有‘高血脂’类药物的毒理/副作用信息

PharmaPendium®

Browse Search My tools | IP-authorized

Safety data search results **整理该适应症上市药物的，各阶段毒理安全信息，同时便捷分类处理** Show/hide columns Save Export

386427 records from Safety data: [Atorvastatin Calcium; Ezetimibe (0) OR Ezetimibe (12699) OR Pravastatin Sodium (8798) OR Lovastatin (2235) OR Fluvastatin Sodium (3323) OR Fenofibrate; Pravastatin Sodium (0) OR Evolocumab (72419) OR Aluminum Nicotinate (0) OR Mipomersen Sodium (291) OR Colesevelam Hydrochloride (3811) OR Cerivastatin Sodium (19014) OR Niacin; Simvastatin (294) OR Pravastatin Sodium; Buffered Aspirin (34) OR Pitavastatin Calcium (1250) OR ...

Filters

Refine search:  
Apply Clear all

Adverse Effects / Toxicity  
Drugs  
Sex  
Serious/Non-serious

Preclinical Data Clinical Data **Post-Marketing Reports (AERS)** All Data

ID	Drug	# Reports	Adverse Events	Reports by Gender	Reports by Age
1	Alirocumab	10926	Myalgia (982) Drug dose omission (672) Muscle spasms (649) Arthralgia (579) Fatigue (563) Pain (538) Influenza like illness (535) Pain in extremity (530) Injection site pain (499) Diarrhoea (477) view all ...	Female (6222) Male (4294)	20+ (7884) <20 (4)
2	Amlodipine Besylate; Atorvastatin Calcium	1685	Death (107) Malaise (100) Dizziness (83) Headache (75) Blood pressure increased (70) Myalgia (70) Oedema peripheral (64) Hypertension (62) Pain (56) Fatigue (53) view all ...	Female (884) Male (623)	20+ (850)

Hide Filters

筛选器整理，分析信息

# 副作用分布研究，辅助临床科研

ParmaPendum还可以辅助整理‘同类型药物’上市后副作用分析热图，辅助分析以上药物的优劣

Heatmap gradation ranges

0.01% - 13.84%   13.85% - 27.68%   27.69% - 41.52%   41.53% - 55.36%   55.37% - 69.22%

[Edit Ranges](#)

Data Display Options

[Show Results And Percentages](#)

Summary Table with Adverse Effects Tree	Alirocumab		Amlodipine Besylate...		Atorvastatin Calcium		Atorvastatin Calcium...		Cerivastatin Sodium		Clofibrate		Colese...
Total	11461	100%	4567	100%	366698	100%	3	100%	21921	100%	236	100%	97...
min & max per column	1 - 4979	0.01% - 43.44%	1 - 1695	0.02% - 37.11%	649 - 129811	0.18% - 35.40%	1 - 2	33.33% - 66.67%	18 - 15174	0.08% - 69.22%	1 - 128	0.42% - 54.24%	34 - 4...
+ Blood and lymphatic system disorders	71	0.62%	219	4.80%	22857	6.23%	0	0.00%	479	2.19%	62	26.27%	34
+ Cardiac disorders	495	4.32%	568	12.44%	51600	14.07%	1	33.33%	3210	14.64%	69	29.24%	71
+ Congenital, familial and genetic disorders	8	0.07%	5	0.11%	1529	0.42%	0	0.00%	62	0.28%	7	2.97%	40
+ Ear and labyrinth disorders	140	1.22%	109	2.39%	6809	1.86%	1	33.33%	294	1.34%	33	13.98%	17
+ Endocrine disorders	22	0.19%	53	1.16%	4043	1.10%	0	0.00%	100	0.46%	12	5.08%	13
+ Eye disorders	302	2.64%	256	5.61%	19298	5.26%	0	0.00%	713	3.25%	47	19.92%	43
+ Gastrointestinal disorders	1599	13.95%	933	20.43%	80670	22.00%	1	33.33%	2799	12.77%	78	33.05%	32
+ General disorders and administration site conditions	4979	43.44%	1695	37.11%	129811	35.40%	2	66.67%	10978	50.08%	128	54.24%	41
+ Hepatobiliary disorders	86	0.75%	134	2.93%	16284	4.44%	0	0.00%	3600	16.42%	23	9.75%	30
+ Immune system disorders	212	1.85%	135	2.96%	12556	3.42%	0	0.00%	184	0.84%	23	9.75%	28
+ Infections and infestations	1108	9.67%	513	11.23%	46236	12.61%	0	0.00%	1248	5.69%	83	35.17%	10
+ Injury, poisoning and procedural complications	1210	10.56%	286	6.26%	24939	6.80%	1	33.33%	281	1.28%	40	16.95%	10
+ Investigations	1579	13.78%	1062	23.25%	82296	22.44%	1	33.33%	3711	16.93%	81	34.32%	22
+ Metabolism and nutrition disorders	238	2.08%	551	12.06%	50991	13.91%	1	33.33%	1380	6.30%	58	24.58%	72
+ Musculoskeletal and connective tissue disorders	3073	26.81%	827	18.11%	75821	20.68%	1	33.33%	15174	69.22%	80	33.90%	20

# 副作用分布细节—层级展示辅助安评分析

Total
min & max per column
+ Blood and lymphatic system disorders
+ Cardiac disorders
+ Congenital, familial and genetic disorders
+ Ear and labyrinth disorders
+ Endocrine disorders
+ Eye disorders
+ Gastrointestinal disorders
+ General disorders and administration site conditions
+ Hepatobiliary disorders
+ Immune system disorders
+ Infections and infestations
+ Injury, poisoning and procedural complications
+ Investigations
+ Metabolism and nutrition disorders
+ Musculoskeletal and connective tissue disorders

副作用还可以进行细节筛选

如果，‘在研药物’ 在某种严重副作用方面，有非常显著的改善，是否会更有希望获批上市？

- Blood and lymphatic system disorders
+ Anaemias nonhaemolytic and marrow depression
- Coagulopathies and bleeding diatheses (excl thrombocyto...
- Bleeding tendencies
Haemorrhagic diathesis
Haemorrhagic disease of newborn
Haemorrhagic disorder
Increased tendency to bruise
Spontaneous haematoma
Spontaneous haemorrhage
+ Coagulation factor deficiencies
+ Coagulopathies
+ Purpuras (excl thrombocytopenic)

Atorvastatin Calcium... <span>▼</span> <span>ⓘ</span>	
3	100%
1 - 2	33.33% - 66.67%
0	0.00%
1	33.33%
0	0.00%
1	33.33%
0	0.00%
0	0.00%
1	33.33%
2	66.67%
0	0.00%
0	0.00%
0	0.00%
1	33.33%
1	33.33%
1	33.33%
1	33.33%

# 副作用分布细节—具体细节辅助DDI研究

每个数据可以点击查看副作用报告细节，便于进行‘DDI’相关研究

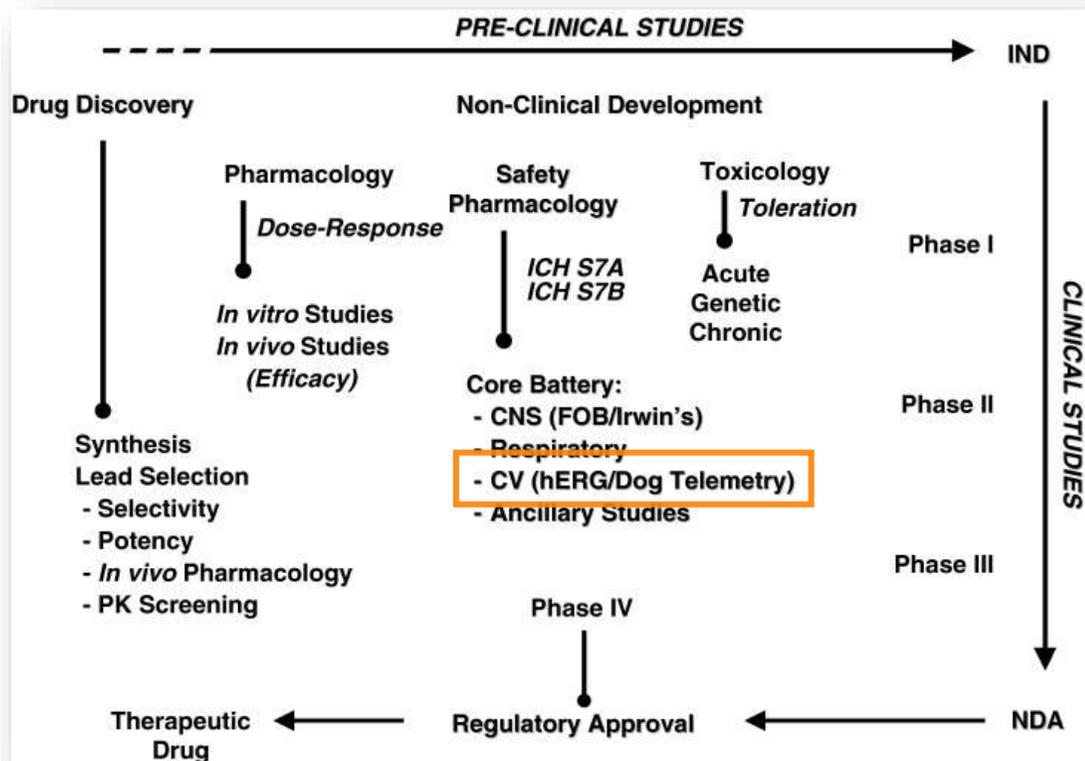
Atorvastatin Calcium... <span>▼</span> <span>i</span>	
3	100%
1 - 2	33.33% - 66.67%
0	0.00%
1	33.33%
0	0.00%
1	33.33%
0	0.00%
0	0.00%
1	33.33%
2	66.67%
0	0.00%
0	0.00%
0	0.00%
1	33.33%
1	33.33%
1	33.33%
1	33.33%

Post-Marketing Reports (AERS)										
ID	AERS Report # <span>▼</span> <span>i</span>	Primary Suspect Drugs <span>▼</span>	Other Administered Drugs <span>▼</span>	Adverse Events <span>▼</span>	Outcomes <span>▼</span>	FDA Date <span>▼</span>	Gender <span>▼</span>	Age (with units) <span>▼</span>	Indications <span>▼</span>	Reporter Occupation <span>▼</span>
1	121530412 <a href="#">View AERS Report</a>	Etanercept	Atorvastatin Calcium; Ezetimibe	Angioedema Feeling abnormal		2016-04-09	Male	49 Year(s)	PRODUCT USED FOR UNKNOWN INDICATION	Pharmacist
2	147827381 <a href="#">View AERS Report</a>	Levothyroxine Sodium	Atorvastatin Calcium; Ezetimibe Levothyroxine Sodium	Alopecia Amnesia Anxiety Arrhythmia Arthralgia Asocial behaviour Asthenia Balance disorder Blood pressure fluctuation Bone pain Decreased interest Depression Disturbance in attention Dizziness Dyspnoea Fatigue Feeling cold Gait disturbance Head discomfort Hyperhidrosis Hypertension Impatience Initial insomnia Irritability Loss of personal independence in daily		2018-04-20	Female	69 Year(s)	PRODUCT USED FOR UNKNOWN INDICATION	Lawyer

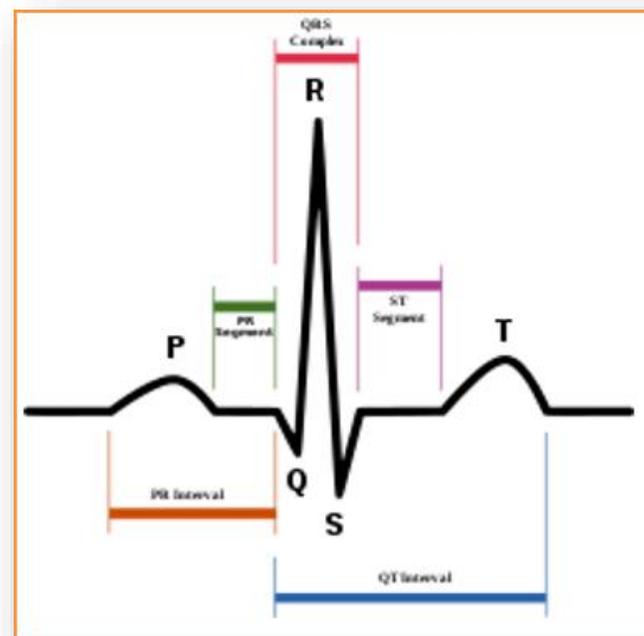
Post-Marketing Reports (AERS)											
ID	AERS Report # <span>▼</span> <span>i</span>	Other Administered Drugs <span>▼</span>	Adverse Events <span>▼</span>	Outcomes <span>▼</span>	FDA Date <span>▼</span>	Gender <span>▼</span>	Age (with units) <span>▼</span>	Indications <span>▼</span>	Reporter Occupation <span>▼</span>	Location <span>▼</span>	Manufa
1	121926041 <a href="#">View AERS Report</a>	Atorvastatin Calcium; Ezetimibe Pantoprazole Sodium Tramadol Hydrochloride Tramadol Hydrochloride	Cell death Confusional state Pneumonia aspiration Poisoning Vomiting Wrong drug administered	Hospitalization	2016-03-18	Female	91 Year(s)		OtherHealthProfessional	FR	PFIZER

# Case 3: QT延长趋势研究

## 安全药理学：QT 信号通路延长趋势研究



QT interval (QT间隔) 在心脏电周期中Q信号和T信号的间隔周期是非常重要的检测指标. 它们的时长指标能够指示快速心率失常的潜在风险



2005年以后, FDA和EMA要求几乎所有的新药都要进行彻底的QT研究, 验证新药分子对于QT interval (间隔) 的影响.



# 筛选-快速分类Safety中的QT研究信息

PharmaPendium®

Browse Search My tools new

Safety data search results

3 records from Safety data: [Palbociclib (2) OR Ribociclib (1)] AND [[Electrocardiogram QT prolonged (3)]]

临床前, 临床, 上市后QT相关的信息分类整理

副作用/毒理筛选器快速定位QT信息

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source
1	Palbociclib	Electrocardiogram QT prolonged	Dog	>3 mg/kg	Single	Intravenous	EMA approval c Assessment Re PDF 4262k
2	Palbociclib	Electrocardiogram QT prolonged	Dog	>10 mg/kg	Single	Intravenous	EMA approval c Assessment Re PDF 4262k
3	Ribociclib	Electrocardiogram QT prolonged	Dog	20 mg/kg	Single	Oral	FDA approval pa Approval Pack PDF 1644k

需要查看实验细节描述

ELSEVIER

# 继续查看临床中的QT信息

PharmaPendium®

检索了Ribociclib临床前QT的问题，继续跟踪其在临床中可能出在的问题

IP-authorized

Safety data search results 5 records from Safety data: [Palbociclib (0) OR Ribociclib (5)] AND [Electrocardiogram QT corrected interval prolonged (5)]

Show/hide columns > Show drugs in... > Save > Export >

Show Filters

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data Preclinical and clinical data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
1	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:17) PDF 4058k	2016
2	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:59) PDF 1681k	2016
3	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	50-1200 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:16) PDF 4058k	2016
4	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/once a day 21 days, then 7 days off	Repeated	Oral	FDA approval package document: Label (Page:5) PDF 767k	2017

# 与剂量相关临床QT问题

检索了Ribociclib临床前QT的问题，继续跟踪其在临床中可能出在的问题

PharmaPendium®

FDA Approval Package

Search this FDA Package

- + Administrative documents
- + Approval Letter
- + Approval Package
- + Chemistry Review
- Label
  - 2017-03-13 PDF(767k)
  - Label 209092/S-001**
- + Letter
- + Other Important Informatio...
- + Review

FDA Approval Package - Ribociclib > Label

Label 209092/S-001

115%

**5 WARNINGS AND PRECAUTIONS**

**5.1 QT Interval Prolongation**

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state  $C_{max}$  following administration at 600 mg once daily dose [see Clinical Pharmacology (12.2)]. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. On the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation [see Adverse Reactions (6)].

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor treatment-related adverse events, including hypokalemia, during KISQALI therapy [see Dosage and Administration (2.2)].

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure,

同时，发现了可能存在的DDI问题

Kisqali+来曲唑组产生晕厥9例（2.7%），安慰剂+来曲唑组3例（0.9%）。Kisqali+来曲唑治疗组，3级低钾血症患者有1例（0.3%）猝死，以及2级QT延长

5 of 17

# 一键获取特定药物Met信息

Ribociclib 在临床前，临床中都出现QT问题，标签中暗示有潜在的DDI问题，快速获取其Met信息，辅助同类型药物开发，实验方案决策

PharmaPendium®

Safety data search results

32 records from Safety data: [Palbociclib (1) OR Ribociclib Succinate (31)] AND [Electrocardiogram QT prolonged (32)]

Filters

Refine search:

Apply Clear all

Adverse Effects / Toxicity

> Investigations (32)

Dose Types

Drugs

Routes of Administration

Sources

Years

Preclinical Data Clinical Data Post-Marketing Reports (AERS) All Data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source
1	Palbociclib	Electrocardiogram QT prolonged	Human	125 mg/day/21 days every 28-day cycle	Repeated	Oral	EMEA approval document: Assessment Report (Page:95) PDF 4262k
2	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:96) PDF 4843k
3	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:18) PDF 2766k
4	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:18) PDF 2766k
5	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:95) PDF 4843k
6	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:96) PDF 4843k
7	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	400-600 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:18) PDF 4058k
8	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:39) PDF 1681k
9	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:91) PDF 4843k
10	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:104) PDF 4843k
11	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:22) PDF 1644k

Show drugs in

Deselect all Select all

Export All drugs in Excel file (.xls)

Show the filtered drugs in other modules. Based on your filtering.

Selected: 1

Palbociclib

Ribociclib Succinate

> Show in Pharmacokinetic Data

> Show in Metabolizing Enz. & Trans. Data

> Show in FAERS Data

> Show in Efficacy Data

# 以特定药物Met信息为基础的DDI研究

PharmaPendium®

Metabolizing Enz. & Transporters search results

143 records from ME&T data: [Ribociclib Succinate (143)]

Ribociclib 临床Met信息中快速分类DDI为题, 如, 来曲唑 (Letrozole)

Filters

Refine search:

Apply Clear all

Drugs

Routes of Administration

Sources

Data type

Enzyme/transporter name

Parent/Metabolite

Test System

Results (qualitative)

Concomitant

Years

Preclinical Data Clinical Data All Data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system	Species	Dose	Route	Substar
1	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)	FMO3	Liver, microsomes	Human	Unreported	In Vitro	Unrepo
2	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)	CYP3A4	Hepatocytes	Human	Unreported	In Vitro	Unrepo
3	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Not applicable	Human	Unreported	Oral	Unrepo
4	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Liver, microsomes	Human	Unreported	In Vitro	Unrepo
5	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Unreported	Human	Unreported	In Vitro	ALL
6	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Hepatocytes	Human	Unreported	In Vitro	Unrepo
7	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Unreported	Human	Unreported	In Vitro	Unrepo
8	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Hepatocytes	Human	Unreported	In Vitro	Unrepo
9	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Unreported	Human	Unreported	In Vitro	ALL
10	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Liver, microsomes	Human	Unreported	In Vitro	Unrepo
11	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Unreported	Human	Unreported	In Vitro	Unrepo
12	Ribociclib Succinate	Parent	Ribociclib	Enzyme Substrate (in vitro)		Hepatocytes	Human	Unreported	In Vitro	Unrepo

Sources

- FDA approval packages (100)
- EMA approval documents (43)

Concomitant

Letrozole

- FDA and EMA approved drugs (118)
  - Antineoplastics (41)
    - Antineoplastics, aromatase inhibitors (41)
      - Letrozole (19)
  - Hormones/hormone modifiers (41)
    - Letrozole (19)

# Letrozole(来曲唑) 与Ribociclib的DDI研究

Ribociclib是2017年新上市CDK抑制剂，来曲唑也可以作为联合用药方案，与其一起治疗乳腺癌。相对来讲与来曲唑相关的DDI是需要重点注意的

伴随药物为来曲唑的，临床研究中所有的PK信息快速获得

Preclinical Data												
ID	Drug				asured	Concomitants	Parameter	Value	Result (quantitative)	Source	Year	
1	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	Letrozole	Letrozole	C ratio	0.899 fold	No	<a href="#">FDA approval package document: Approval Package (Page:26)</a> <a href="#">View Full Study PDF 2766k</a>	2016
2	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	Letrozole	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:26)</a> <a href="#">View Full Study PDF 2766k</a>	2016
3	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	PARENT	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:26)</a> <a href="#">View Full Study PDF 2766k</a>	2016
4	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	PARENT	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:14)</a> <a href="#">View Full Study PDF 2766k</a>	2016
5	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	PARENT	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:18)</a> <a href="#">View Full Study PDF 2766k</a>	2016
6	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	PARENT	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:5)</a> <a href="#">View Full Study PDF 4058k</a>	2016
7	Ribociclib Succinate	ot applicable	Human	Unreported	Oral	PARENT	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Label (Page:13)</a> <a href="#">View Full Study PDF 767k</a>	2017
8	Ribociclib Succinate	ot applicable	Human	Unreported	Oral	Letrozole	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Label (Page:13)</a> <a href="#">View Full Study PDF 767k</a>	2017
9	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	Letrozole	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:26)</a> <a href="#">View Full Study PDF 2766k</a>	2016
10	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	Letrozole	Letrozole	Cmin ratio	0.932 fold	No	<a href="#">FDA approval package document: Approval Package (Page:26)</a> <a href="#">View Full Study PDF 2766k</a>	2016
11	Ribociclib Succinate	ot applicable	Human	Unreported	Unreported	Letrozole	Letrozole	PK (unspecified)		No	<a href="#">FDA approval package document: Approval Package (Page:14)</a> <a href="#">View Full Study PDF 2766k</a>	2016

点击查看细节

# Letrozole(来曲唑) 与Ribociclib的DDI—细节研究

Approval Package 209092/S-000 Part 02

175% 0.899 1/1 Go

ribociclib once daily dose and there is no need for dose adjustment.

## DDI between ribociclib and aromatase inhibitors

Letrozole: Clinical data suggested no DDI potential between ribociclib and letrozole. Ribociclib has no clinically relevant effect on letrozole PK based on a comparison of letrozole PK data between letrozole in combination with ribociclib and letrozole in combination placebo in Study A2301. letrozole C troughs were similar between these treatment arms (GMR: 0.932; 90% CI: 0.815, 1.07). Plasma concentrations at 2 h post-dose were also similar between these treatment arms (GMR: 0.899; 90% CI: 0.815, 0.992). In a population analysis including 208 patients with cancer, 47 patients had concomitant use of letrozole. Concomitant use of letrozole had no significant effect on ribociclib PK (See section 13.4.3 for detail).

临床研究中显示，来曲唑与Ribociclib不存在DDI问题

Anastrozole: Clinical data suggested no clinically relevant DDI between ribociclib and anastrozole. Concentrations of ribociclib and anastrozole administered as coadministered drugs (Study E2301) overlapped with concentrations of ribociclib from Study X2101 (Table 11) and anastrozole administered as a single agent (Table 12).

Table 11. Cross study comparison of steady state ribociclib PK parameters at 600 mg QD dose

PK parameter	Statistics	E2301	E2301	X2101 [Ribociclib single agent] <sup>1</sup>
		[Ribociclib + letrozole] C1D15	[Ribociclib + letrozole] C3D15	
Predose (ng/mL)	n	5	15	64
	Mean (± SD)	742 (± 578)	485 (± 347)	732 (± 586)
	Geo-mean	600	372	558
	CV% geo-mean	80	110	91
C <sub>max</sub> (ng/mL)	n	-	6	57
	Mean (± SD)	-	2470 (± 1022)	2130 (± 1260)
	Geo-mean	-	2334	1820
	CV% geo-mean	-	36	62.4

# 继续探索Ribociclib可能的DDI问题

PharmaPendium®

Metabolizing Enz. & Transporters search results

143 records from ME&T data: [Ribociclib Succinate (143)]

Filters ▾

Refine search:

Apply Clear all

Drugs ▾

Routes of Administration ▾

Sources ▾

Data type ▾

Enzyme/transporter name ▾

Parent/Metabolite ▾

Test System ▾

Results (qualitative) ▾

Concomitant ▾

Years ▾

Preclinical Data Clinical Data All Data

Results (qualitative)

- No (42)
- Yes (44)
- Blank (Unreported) (57)

Enzyme/Transporter	Test system	Species	Dose	Route	Substar
FMO3	Liver, microsomes	Human	Unreported	In Vitro	Unrepo
CYP3A4	Hepatocytes	Human	Unreported	In Vitro	Unrepo
CYP3A4	Not applicable	Human	Unreported	Oral	Unrepo
CYP3A4	Liver, microsomes	Human	Unreported	In Vitro	Unrepo
FMO3	Unreported	Human	Unreported	In Vitro	ALL
CYP3A4	Hepatocytes	Human	Unreported	In Vitro	Unrepo
CYP3A4	Unreported	Human	Unreported	In Vitro	Unrepo
FMO3	Hepatocytes	Human	Unreported	In Vitro	Unrepo

结果定性筛选器

筛选有伴随药物

Preclinical Data Clinical Data All Data

ID	Drug	System	Species	Dose	Route	Substance measured	Concomitants	Parameter	Value	Result (qualitative)	Source	Year
1	Ribociclib Succinate	applicable	Human	600 mg, single	Unreported	PARENT	Rifampin	Cmax decrease	81%	Yes	FDA approval package document: Approval Package (Page:25) View Full Study PDF 2766k	201
2	Ribociclib Succinate	applicable	Human	600 mg, single	Unreported	PARENT					FDA approval package document: Approval Package (Page:25) View Full Study PDF 2766k	201
3	Ribociclib Succinate	applicable	Human	400 mg/d, for 8 days	Oral	Caffeine	Midazolam Hydrochloride	AUC increase	20%	Yes, Minimal	FDA approval package document: Label (Page:13) View Full Study PDF 767k	201
4	Ribociclib Succinate	applicable	Human	400 mg/d	Unreported	Midazolam	Midazolam Hydrochloride	AUC ratio	3.8 fold	Yes	FDA approval package document: Approval Package (Page:20) View Full Study PDF 2766k	201

伴随药物为‘咪达唑仑’存在是AUC 增加

ELSEVIER

# 继续探索Ribociclib可能的DDI问题—细节

同种方法筛选获取的其他细节

27%, respectively. A model  
60%, respectively.

会被Ribociclib影响的药，如midazolam镇静类药物

## Drugs That Are Affected By KISQALI

**CYP3A4 and CYP1A2 substrates:** A drug interaction trial in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam  $C_{max}$  and  $AUC_{inf}$  3.8-fold and 3.8-fold, respectively. Administration of ribociclib at 600 mg once daily is predicted to increase midazolam  $C_{max}$  and  $AUC_{inf}$  by 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of 400 mg ribociclib on caffeine was minimal, with  $C_{max}$  decreased by 10% and  $AUC_{inf}$  increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at 600 mg ribociclib once daily dose.

**Gastric pH-elevating agents:** Coadministration of ribociclib with drugs that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not identified in a population PK analysis and was not predicted using physiology based PK models.

**Letrozole:** Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following coadministration of the drugs.

**Anastrozole:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following coadministration of the drugs.

**Exemestane:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following coadministration of the drugs.

## In vitro Studies

**Effect of ribociclib on CYP enzymes:** In vitro, ribociclib was a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. In vitro evaluations indicated KISQALI has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 at clinically relevant concentrations. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP3A4 and no induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 at clinically relevant concentrations.

**Effect of ribociclib on transporters:** In vitro evaluations indicated that KISQALI has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. KISQALI does not inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

**Effect of transporters on ribociclib:** Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses.

000 Part 02

rifampin 1/2

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209092  
KISQALI (ribociclib).

clearance is predicted  
Section 13.3.5.4 for  
ritonavir provided a  
without a CYP3A4 inh  
a strong CYP3A4 inh

与rifampin（抗生素）药物作用研究，体现Ribociclib会被CYP3A的诱导剂影响而降低AUC,应避免与CYP酶诱导剂一起用药

in (See  
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stration  
t use of  
d.

CYP3A Inducers: Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma AUC of ribociclib by 89%. The concomitant use of strong CYP3A4 inducers with ribociclib should be avoided.

CYP3A Substrates: Coadministration of midazolam (CYP3A4 substrate) with multiple doses of 400 mg ribociclib increased the midazolam exposure by 3.8-fold. Simulations using PBPK models suggested that ribociclib given at dose of 600 mg once daily is expected to increase the midazolam AUC by 5.2-fold. Caution is recommended when ribociclib is administered with CYP3A substrates with a narrow therapeutic index.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no DDI between ribociclib and letrozole.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and anastrozole.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and exemestane.

# 今天的内容

- ParmaPendium数据库的简介
  - PharmaPendium中的内容
  - PharmaPendium中的检索模块与基本应用
- ParmaPendium数据库的应用
  - 涉及药物的安全性、药效、DMPK数据获取的应用
    - 单一/一类药物数据的获取
    - 涉及特殊安全性研究（QT延长毒性）的相关报道的获取
  - 涉及新药申请方面的应用
    - 如何为非验证性“替代临床终点”提供证据支持
    - 如何为因“种族差异”导致的剂量差别寻找证据支持
  - Met代谢数据检索及DDI预测的应用
    - 抗肿瘤药物的代谢酶或转运体活性显著变化的信息检索
    - 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢
    - DDI



## 涉及新药申请方面的应用

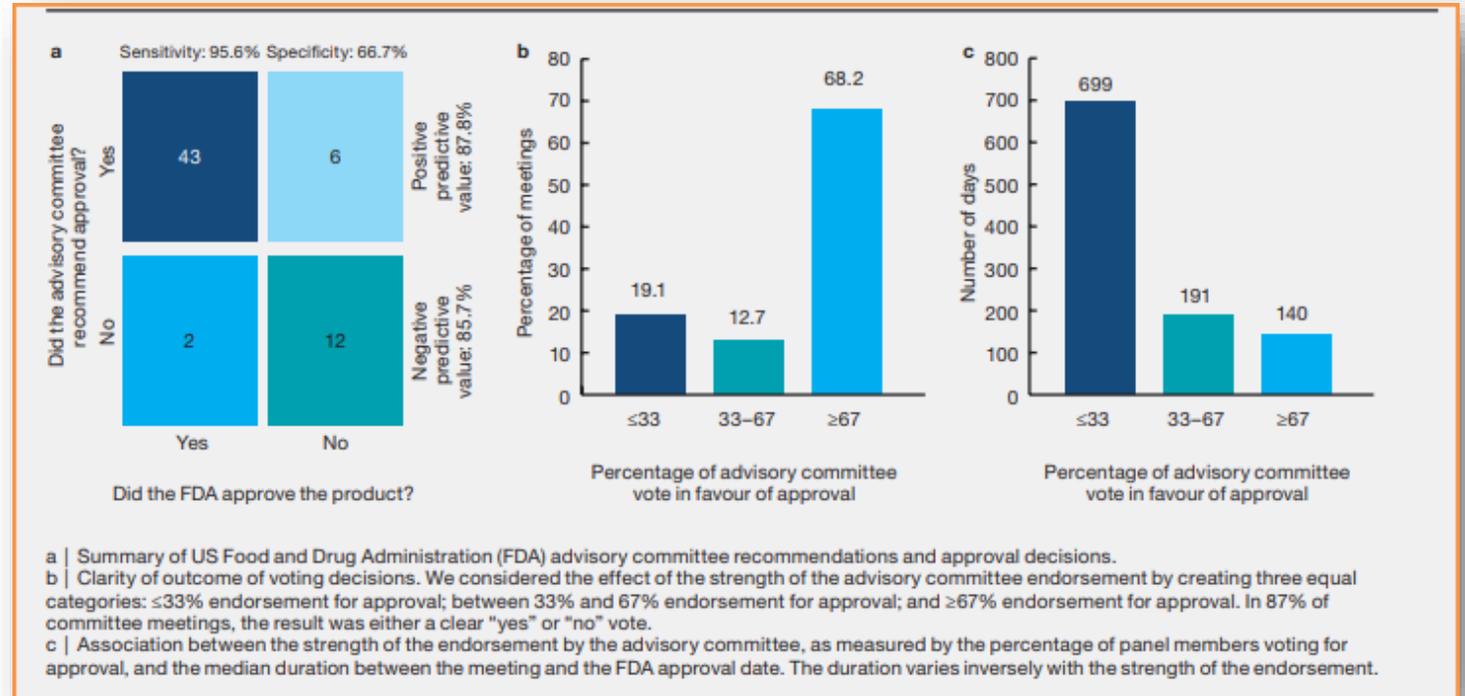
**Case 3:** 如何为“非验证替代临床终点”提供证据支持

**Case 4:** 如何为因“种族差异”导致的剂量差别寻找证据支持



# FDA 评审委员会会议档案检索的重要性

- 在IDN/DNA申请过程中FDA/EMA会参考咨询委员会的意见来决定是否批准申请
- FDA/EMA咨询委员会专家会根据自己的不同见解提出需要解答的问题。
- 通过收集已有审批通过的药物的评审报告,能够参考推测评审委员会可能提出的问题一定程度上使申请过程更加的流畅
- 在FDA官网检索, AC报告并不在 approval package中, 且只能按年限检索, 且一次只能阅读一份报告



# FDA-AC---报告快速检索

如何收集用于治疗AML（急性髓细胞白血病）相关药物的FDA AC 报告

“Acute myeloid leukemia” 进行free text检索

Quick Search

All These Sources  Include synonyms

Search

Find adverse effect/toxicity data across preclinical, clinical, post-market reports and ...

- Pharmacokinetic Data
- Metabolizing Enz. & Trans. Data
- Drug Safety Data
- Chemistry Search
- Efficacy Data
- Activity Data

Search results

2033 records from Documents: ["Acute myeloid leukemia" with synonyms]

Jump to: page 1 Show/hide columns

ID	Document with context	Drug name	Source
1	Q&A EMA/COMP/86675/2005 Rev.3 PDF 117k ... AB, Sweden, in October 2012. What is acute myeloid leukemia? Acute myeloid leukemia is a disease in ...	Histamine Dihydrochloride	EMA approval documents
2	Background Part 05 (Oncologic Drugs Advisory Committee) PDF 969k ... /etoposide; ALFA=Acute Leukemia French Association; AML=acute myeloid leukemia; AraC=cytarabine; APL=acute ...	N/A	FDA Advisory Document
3	Questions Part 02 (Oncologic Drugs Advisory Committee) PDF 206k ... novel poor-risk acute myeloid leukemia (AML). BACKGROUND - Single arm studies 049 and 033 o 28 - 29 ...	N/A	FDA Advisory Document
4	Microbiology Review 021174/S-000 PDF 259k ... intended to treat patients with relapsing acute myeloid leukemia NDA 21-174 Microbiologist's Review #2 (AMM) ...	Gemtuzumab Ozogamicin	FDA approval
5	Letter 103353 PDF 200k ... in patients with acute Myeloid Leukemia has been approved. Please submit three copies of final ...	Filgrastim	FDA approval
6	Letter 103353/S-1036 PDF 201k ... Acute Myeloid Leukemia has been approved. Please submit three copies of final printed labeling at the ...	Filgrastim	FDA approval
7	Microbiology Review 021174 PDF 223k ... intended to treat patients with relapsing acute myeloid leukemia NDA 21-174 Microbiologist's Review #2 (AMM) ...	Gemtuzumab Ozogamicin	FDA approval

Filters

Refine search:

Drugs

Sources

- FDA approval packages (1281)
- EMA approval documents (276)
- FDA Advisory Committee Documents (27)
- DESI documents (3)
- Meyler's (25)
- Mosby's Drug Consult™ (27)

结果集中，筛选 'sources' 的中的AC报告

# FDA-AC-快速分类不同评审的结果

进一步分类用于治疗AML（急性髓细胞白血病）相关肿瘤药物AC 报告

Sources

- FDA approval packages (1281)
- EMA approval documents (276)
- FDA Advisory Committee Documents (27)
- DESI documents (3)
- Meyler's (25)
- Mosby's Drug Consult™ (27)

Years

- Medical Imaging Drugs Advisory Committee Documents (1)
- Nonprescription Drugs Advisory Committee Documents (1)
- Oncologic Drugs Advisory Committee Documents (12)
- Agenda (12)
- Background (36)
- Briefing (72)
- Minutes (10)
- Other documents (1)
- Questions (12)
- Slides (78)
- Transcript (62)
- Waiver (3)

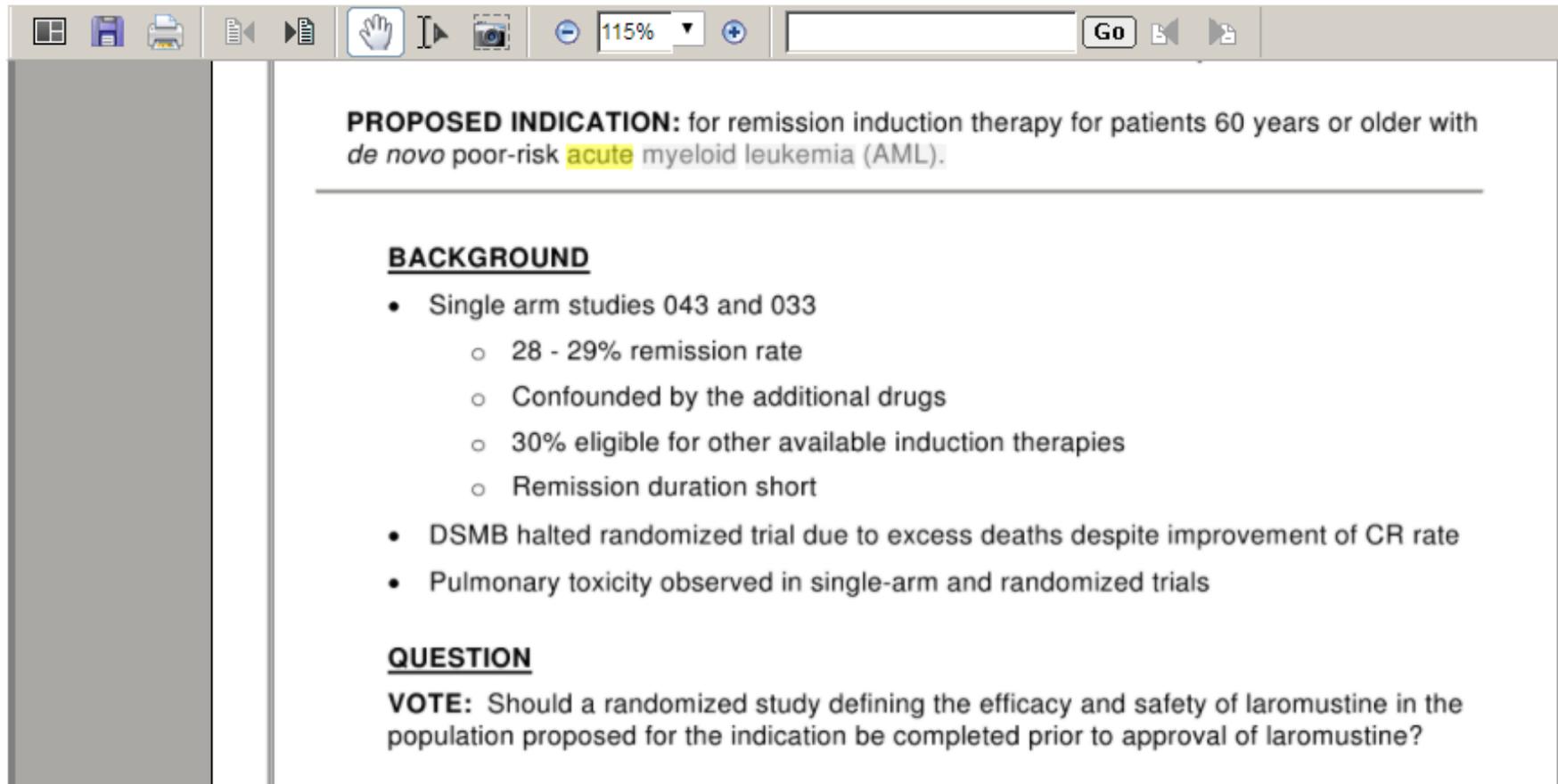
通过筛选器，快速便捷的得到了，关于治疗AML的肿瘤药物的AC报告结果

ID	Document with context	Drug name	Source	Year
1	Background Part 05 (Oncologic Drugs Advisory Committee) PDF 969k ... /etoposide; ALFA=Acute Leukemia French Association; <b>AML-acute myeloid leukemia</b> ; AraC=cytarabine; APL=acute ...	N/A	FDA Advisory Committee Documents	2017
2	Questions Part 02 (Oncologic Drugs Advisory Committee) PDF 206k ... novo poor-risk <b>acute myeloid leukemia (AML)</b> . BACKGROUND - Single arm studies 043 and 033-e-28 - 29 ...	N/A	FDA Advisory Committee Documents	2009
3	Agenda Part 02 (Oncologic Drugs Advisory Committee) PDF 242k ... novo poor-risk <b>acute myeloid leukemia (AML)</b> . 1:25 p.m. Sponsor Presentation Vion Pharmaceuticals, Inc ...	N/A	FDA Advisory Committee Documents	2009
4	Agenda Part 01 (Oncologic Drugs Advisory Committee) PDF 242k ... years or older with de novo poor-risk <b>acute myeloid leukemia (AML)</b> . 1:20 p.m. Opening Remarks Richard ...	N/A	FDA Advisory Committee Documents	2009
5	Background Part 02 (Oncologic Drugs Advisory Committee) PDF 219k ... progressed to <b>AML</b> . Page 25, Myelodysplastic Syndrome; <b>Acute Myeloid Leukemia</b> . In the paragraph discussing ...	N/A	FDA Advisory Committee Documents	2014
6	Background Part 06 (Oncologic Drugs Advisory Committee) PDF 703k ... idarubicin as induction for pediatric <b>acute myeloid leukemia</b> ; results from Study <b>AML-BFM</b> 2004. Blood 2013;122 ...	N/A	FDA Advisory Committee Documents	2017

# FDA-AC---评审委员会评审意见细节

FDA Advisory Committee - Oncologic Drugs Advisory Committee > 2009-Sep-01

## Questions Part 02



The screenshot shows a PDF document viewer interface. At the top, there is a toolbar with icons for window, save, print, back, forward, search, zoom in, zoom out, and a search box with a 'Go' button. The zoom level is set to 115%. The main content area displays the following text:

**PROPOSED INDICATION:** for remission induction therapy for patients 60 years or older with *de novo* poor-risk acute myeloid leukemia (AML).

---

**BACKGROUND**

- Single arm studies 043 and 033
  - 28 - 29% remission rate
  - Confounded by the additional drugs
  - 30% eligible for other available induction therapies
  - Remission duration short
- DSMB halted randomized trial due to excess deaths despite improvement of CR rate
- Pulmonary toxicity observed in single-arm and randomized trials

**QUESTION**

**VOTE:** Should a randomized study defining the efficacy and safety of laromustine in the population proposed for the indication be completed prior to approval of laromustine?

随机对照组实验,能够验证 laromustine在前期递交申请中的提到的对相应目标人群适应症的治疗药效和安全性吗?

# Case 3: 如何为糖尿病“替代临床终点”提供证据支持

Free text检索便捷获取原文细节信息

PharmaPendium® Browse Search My tools

## Advanced search

Search criteria

Find results

... with **all** the words:

... within at least  words of one another

... with **at least** one of the words:

... **without** the words:

Include synonyms

### Advanced Search Tips

- Use the 1st field for proximity searching. Proximity terms NEAR operator. The proximity search does NOT search for synonyms Wildcards (\* or ?) can be used here. The number at the end (distance) is how close in the document phrases to be. The maximum distance for this search is 250. Proximity Searches can also be done on the Quick Search page. [Syntax: term1 NEAR[n] term2, termN = Distance]

PharmaPendium® Browse Search My tools new | IP-authorized

Search results 126 records from Documents:  [QUERY DETAILS]

Refine search results:

Jump to:  Show/hide columns Show drugs in... Save Export Search in EMBASE

ID	Document with context	Drug name	Source	Year
1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk): <b>diabetes mellitus aggravated diabetes mellitus exacerbated worsening of</b> ...	<b>Fenofibrate; Pravastatin Sodium</b>	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... <b>diabetes mellitus</b> . N Engl J Med. 1999;341:1127-33. 4. Frank RN. <b>Diabetic</b> retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical I:\7630dft.doc 02/13/08 Guidance for Industry <b>Diabetes Mellitus</b> ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any <b>diabetic</b> AE <b>Diabetes mellitus</b> Blood glucose	N/A	FDA Advisory Committee Documents	2009

# 获得FDA 评审委员会对于临床终点的各种信息

PharmaPendium®

Browse Search My tools new

Search results 126 records from Documents: [surrogate,validated=5] AND (diabetes) with synonyms [QUERY DETAILS]

Refine search results: Apply Clear All

Hide Filters

快速分类评审委员会会议档案中细节信息  
辅助决策临床终点的选择, 临床方案设计

/hide columns Show drugs in... Save Export Search in EMBASE

ID	Document with context	Drug name	Source	Year
1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk): <b>Diabetes mellitus aggravated</b> , <b>diabetes mellitus exacerbated</b> , <b>worsening of</b> ...	<b>Fenofibrate;</b> <b>Pravastatin Sodium</b>	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... <b>diabetes mellitus</b> . N Engl J Med. 1999;341 :1127-33. 4. Frank RN. <b>Diabetic</b> retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical I:\7630dft.doc 02/13/08 Guidance for Industry <b>Diabetes Mellitus</b> ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any <b>diabetic</b> AE <b>Diabetes mellitus</b> Blood glucose	N/A	FDA Advisory Committee Documents	2009

# 快速获取特定原文中的临床终点信息

The screenshot displays the PharmaPendium website interface. At the top, there is a navigation bar with 'PharmaPendium®' on the left and 'Browse', 'Search', and 'My tools' in the center. A search bar is active with the text 'surrogate' and a 'Go' button. The page title is 'EMA Approval Package - Fenofibrate; Pravastatin Sodium > Assessment Report'. A sidebar on the left contains a search box and a list of document sections: 'All Authorized Presentations', 'ANNEX I', 'Assessment Report' (expanded to show a PDF file '2011-01-01 PDF(756k) Assessment Report EM...'), 'Marketing Authorization Steps', 'Other Information from EMA', and 'Public Assessment Report'. The main content area shows a text snippet from the document: '...fenofibrate/simvastatin combination therapy to reduce cardiovascular events in the majority of dyslipidaemic high CV risk patients with type 2 diabetic patients. Indeed, only beneficial effects on cardiovascular endpoints were observed in patients with high TG and low HDL-C values. This has also been extensively discussed during Article 31 referral on fenofibrate. Thus, finally, only an indication that will be limited to this specific population subgroup can be granted by the CHMP.' Below this, a section titled 'Benefit-risk balance' is highlighted with an orange box and the Chinese text '风险-收益'. The text under this section discusses the benefit-risk balance based on provided data, mentioning 'surrogate endpoints' and the ACCORD study. A sub-section '2.8.1. Discussion on the benefit-risk balance' is also visible, with text starting 'Based on the provided data and the rationale above, Pravafenix is aimed to offer an alternative to a specifically targeted population; i.e. high CHD-risk adult patients with mixed dyslipidaemia characterised by high TG and low HDL-C whose LDL-C are adequately controlled while on a treatment with pravastatin 40mg monotherapy.'

# “非验证替代终点”原文信息的检索

## Advanced search

### Search criteria

### Find results

... with **all** the words:

... within at least  words of one another

... with **at least** one of the words:

... **without** the words:

Include synonyms

### Advanced Search Tips

- Use the 1st field for proximity searching. Proximity terms (NEAR operator). The proximity search does NOT search for synonyms. Wildcards (\* or ?) can be used here. The number at the end (distance) is how close in the document phrases to be. The maximum distance for this search is 20. Proximity Searches can also be done on the Quick Search!



ELSEVIER

PharmaPendium®

Browse ▾ Search ▾ My tools <sup>new</sup>



Search results 12 records from Documents:  [QUERY DETAILS]

快速收集评审委员会档案中‘非验证终点’的细节

Jump to:

Show/hide columns >

Show drugs in... >

Save

ID	Document with context	Drug name ▾	Source ▾	Year ▾
1	<a href="#">Briefing 4355 Part 01 (Blood Products Advisory Committee) PDF 432k</a> ... <b>unvalidated surrogate</b> endpoint at this time. For the secondary endpoints attack severity and attack duration ...	N/A	FDA Advisory Committee Documents	2008
2	<a href="#">Briefing 4355 Part 02 (Blood Products Advisory Committee) PDF 466k</a> ... addition, the secondary endpoint of C1INH levels must be considered an <b>unvalidated surrogate</b> endpoint at ...	N/A	FDA Advisory Committee Documents	2008
3	<a href="#">Approval Package 020604/S-040 PDF 2381k</a> ... -related events including new onset <b>diabetes mellitus</b> and <b>diabetic</b> ketoacidosis led to a language upgrade ...	<b>Somatropin, Biosynthetic</b>	FDA approval packages	2011
4	<a href="#">Background Part 17 (Cardiovascular and Renal Drugs Advisory Committee) PDF 2057k</a> ... of 224 Tolvaptan (OPC-41061) NDA 204441 that TKV is an <b>unvalidated surrogate</b> , TKV was chosen as the ...	N/A	FDA Advisory Committee Documents	2013
5	<a href="#">Transcript Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 2384k</a> ... to understand 16 that concluding that an effect on an <b>unvalidated 17 surrogate</b> will	N/A	FDA Advisory Committee Documents	2012

# 获取原文中的细节描述

PharmaPendium® Browse Search My tools IP-authorized

FDA Advisory Committee

FDA Advisory Committee - Cardiovascular and Renal Drugs Advisory Committee > 2013-Aug-05

Background Part 17

Search this FDA Advisory Coi

- 2013-08-05 PDF(2057k) Background Part 17
- 2013-08-05 PDF(2581k) Background Part 18
- 2013-08-05 PDF(1603k) Background Part 19
- 2013-08-05 PDF(471k) Background Part 20
- 2013-08-05 PDF(3399k) Background Part 21
- 2013-08-05 PDF(644k) Background Part 22
- 2013-08-05 PDF(315k) Minutes
- 2013-08-05 PDF(202k) Other documents
- 2013-08-05 PDF(249k) Questions Part 01
- 2013-08-05 PDF(235k)

progression. Its ability to detect changes over a relatively short (3-year) period of the disease's slow course of progression permitted estimation of power for what would be a clinically relevant degree of change (20% reduction). While the sponsor acknowledges

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非常规‘临床终点’细节，辅助方案设计

Tolvaptan (OPC-41061) NDA 204441

that TKV is an unvalidated surrogate, TKV was chosen as the primary endpoint for this trial because if no effect were seen in TKV, it was believed no other clinical benefits would be conveyed to patients.

The TKV endpoint methodology established in the NIH CRISP program was adapted for the pivotal study and validated.<sup>5</sup> Total kidney volume also served as a mechanism for prognostic enrichment: data available during protocol design supported an association of

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# 获得FDA 评审委员会对于临床终点的各种信息

PharmaPendium®

Browse Search My tools new

Search results 126 records from Documents: [surrogate,validated=5] AND (diabetes) with synonyms [QUERY DETAILS]

Refine search results: Apply Clear All

Hide Filters

快速分类评审委员会会议档案中细节信息  
辅助决策临床终点的选择, 临床方案设计

/hide columns Show drugs in... Save Export Search in EMBASE

ID	Document with context	Drug name	Source	Year
1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk): <b>Diabetes mellitus aggravated</b> , <b>diabetes mellitus exacerbated</b> , <b>worsening of</b> ...	<b>Fenofibrate;</b> <b>Pravastatin Sodium</b>	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... <b>diabetes mellitus</b> . N Engl J Med. 1999;341 :1127-33. 4. Frank RN. <b>Diabetic</b> retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical I:\7630dft.doc 02/13/08 Guidance for Industry <b>Diabetes Mellitus</b> ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any <b>diabetic</b> AE <b>Diabetes mellitus</b> Blood glucose	N/A	FDA Advisory Committee Documents	2009

# Case 4:如何为因“种族差异”导致的针对不同种族的剂量差别寻找证据支持

内在和外在的因素会影响PK/PD

## 4. ICH E5, Ethnic Factors in the Acceptability of Foreign Clinical Data

This guidance provides descriptions of PK and PD studies and expresses PD endpoints as safety and/or efficacy measures of activity thought, but not documented, to be related to clinical benefit (biomarkers), surrogate endpoints, and clinical benefit endpoints. The guidance further defines a PD study as one that describes the relationship between a pharmacological effect or clinical benefit effect in relation to dose or drug concentration. The guidance establishes a classification system of intrinsic (genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction) and extrinsic (medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, practices in clinical trial design and conduct, socioeconomic status, compliance with medication) ethnic factors that can affect safety, efficacy, dosage, and dosage regimen determinations. The guidance provides an additional set of factors that indicate whether a drug may be sensitive to ethnic factors (linear PK, flat PD curve, wide therapeutic range). It focuses on the bridging studies that may be critical for an application in a new region based on a clinical data package developed in another region. These bridging studies range from those that establish similarity of exposure-response relationship in the two regions for a well-established PD effect (e.g., ACE inhibition or short-term blood pressure response) to a controlled trial in the new region, preferably a dose-response study, using the pertinent clinical endpoint.

在FDA的知道文件当中注明，种族因素是一个影响药效和安全的重要因素，因此在设计临床实验，以及IND, NDA申请的时候需要考虑这些因素对在研药物的影响，那么快速高效的收集相关信息，有助于决策

# Pharmacokinetic---以药物种类为基础检索

检索不同区域种族信息对于抗肿瘤药物（包括单抗）的Cmax（血药峰浓度）数据的影响

The screenshot displays the PharmaPendium search interface. At the top, there is a 'Quick Search' section with a dropdown menu for 'All These Sources' and a search input field containing 'e.g. Coronar\* artery disorders'. Below this, there is a checkbox for 'Include synonyms'. The main search area is titled 'Find adverse effect/toxicity data across preclinical' and contains four icons: 'Pharmacokinetic Data', 'Metabolizing Enz. & Trans. Data', 'Chemistry Search', and 'Efficacy Data'. A search bar at the top right contains the text 'antineoplastics, monoclonal antibodies'. Below the search bar, a dropdown menu shows the search results, with 'Antineoplastics, monoclonal antibod...' selected. The main content area displays the search results for 'Antineoplastics, monoclonal antibodies'. It includes a list of 'Drugs' such as Ado-Trastuzumab, Emtansine, Alemtuzumab, Atezolizumab, Avelumab, Bevacizumab, Blinatumomab, Brentuximab Vedotin, Catumaxomab, Cetuximab, Daratumumab, and a 'view all ...' link. Under 'Biology data', there is a link for 'view Pharmacokinetic Data' which is highlighted. Under 'Primary targets', there is a list of targets including CD19 Antigen, CD20 Antigen, CD3 Antigen, CD33 Antigen, CD38 antigen, CD52 Antigen, EGFR Receptor 2 Protein (HER2), Epidermal Growth Factor (EGFR) Receptors, ErbB1, and Glycolipid GD2, with a 'view all ...' link at the bottom.

通过PP能够快速通过‘某一类药物’搜集到 approval文件中的PK数据，antineoplastics

# Pharmacokinetic---参数的快速限定

通过filter快速限定需要评估的药物和参数

PharmaPK  
Pharmacokinetic data search results  
8043 records from PK Data: [Antineoplastics, monoclonal antibodies (8043)]

Filters  
Refine search: [Apply] [Clear all]

Parameter ranges

- Absorption (3250)
  - Bioavailability (4)
- Concentrations (2890)
  - C (314)
  - Cavg (138)
  - Cmax (1536)
  - Cmin (902)
- + Time values (356)

ID	Drug	Species	Route	Parameter	Parameter Value	SD	t
1	Ado-Trastuzumab Emtansine	Human	Intravenous	CL(antibody-drug conjugates)	0.68 L/d		
2	Ado-Trastuzumab Emtansine	Human	Intravenous	T1/2(conjugate (ADC))	4.0 d		
3	Ado-Trastuzumab Emtansine	Human	Intravenous	Vc(antibody-drug conjugates)	3.13 L		

在筛选的结果集里面可以进一步导出excel表格便于辅助分析

Pharmacokinetic data search results  
71 records from PK Data: [Antineoplastics, monoclonal antibodies (71)] AND [Panitumumab (71)] AND [Cmax (71) ug/g]

Parameter ranges

- Nivolumab
- Obinutuzumab
- Ofatumumab
- Panitumumab
- Olaratumab
- Pertuzumab
- Ramucirumab
- Ranibizumab

ID	Drug	Species	Study Group	Dose	Route	Cmax		
1	Panitumumab	Human	advanced solid tumors	0.75 mg/kg	Intravenous	Cmax		
2	Panitumumab	Human	advanced solid tumors	1 mg/kg	Intravenous	Cmax		
3	Panitumumab	Human	advanced solid tumors	1.5 mg/kg	Intravenous	Cmax		
4	Panitumumab	Human	advanced solid tumors	2 mg/kg	Intravenous	Cmax		
5	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	53.0ug/mL	week 26
6	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	121.0 ug/mL	week 44
7	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	56.3 ug/mL	

Export data

Deselect all columns | Select all columns

Select columns for export

- Chemical Structure
- Radiolabelled
- Species
- Study Number
- Study Group
- Study Name
- #N
- Sex
- Age
- Dose
- Duration
- Route
- Assay
- Parameter
- Parameter Value
- Parameter Normalized Value (only standard units are normalized)
- Parameter Normalized Unit (only standard units are normalized)
- SD
- t
- Concomitant
- Comments
- Source
- Year

> Export as Excel document (.xls)  
> Export as Excel document (.xlsx)  
> Export as tab delimited (.tsv)  
> Export as comma delimited (.csv)



# Pharmacokinetic---原始文献查看

FDA Approval Package - Panitumumab > Clinical Pharmacology and Biopharmaceutics Review  
Clinical Pharmacology and Biopharmaceutics Review 125147/S-0000

115% 13/27 Go

of arithmetic mean values expressed as a percentage.  
\*Study 20030138 for the 2.5 mg/kg group and Study 20030251 for the 6 mg/kg group.  
Source: Nofumamab/Docetaxel/irinotecan/PAAD Candidates/Development/AMG 554 -  
ABX-EGF/Predicted Non-Study Specific/PK/MS/Submission/ELAClinical/Supporting data/irw/irw/vr

**Conclusions:**  
Results for the 12 subjects enrolled in this study indicate that commercial scale, CHO-derived Panitumumab at 2.5 mg/kg QW and 6.0 mg/kg Q2W was well tolerated as monotherapy in Japanese subjects with advanced solid tumors. No DLT(s) was observed in either 2.5 mg/kg QW or 6.0 mg/kg Q2W dosing cohorts up to 4 weeks after the first Panitumumab infusion. Adverse events consisted primarily of mild or moderate events in the skin and gastrointestinal body systems. Because limited data were available after week 4, time to PK steady-state could not be assessed for either cohort. The overall Panitumumab PK profiles are slightly lower than those observed in

78

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non-Japanese subjects; however, based on the limited sample size in these 2 dose cohorts (6 subjects in each cohort), conclusions on the comparison of the PK between non-Japanese and Japanese subjects cannot be made at this time. Additional PK data in the Japanese population will be collected from the 9 mg/kg Q3W. No postdose blood samples tested seropositive for human antibodies to Panitumumab in either cohort as of data cutoff.

**Study 20025404**  
A Two Part, Multiple Dose Clinical Trial of the Safety and Efficacy of ABX-EGF in Combination with Paclitaxel and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer

**Methodology:**  
Open-label, multicenter, sequential dose escalation of Panitumumab with paclitaxel and carboplatin chemotherapy in subjects with advanced NSCLC. Subjects received up to 6 cycles of chemotherapy given every 3 weeks with Panitumumab doses of 1.0, 2.0, or 2.5 mg/kg IV once weekly. After 18 weeks of chemotherapy and Panitumumab, subjects with an objective tumor response or stable disease could receive up to 18 additional weeks of Panitumumab monotherapy (36 weeks total).  
**Number of Subjects Planned:** 5 to 10 per dose cohort, or a maximum of 30 subjects total

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PP中的‘text searching’功能可以快速把原文中的相关细节找到，便于参考

FDA Approval Package - Panitumumab > Clinical Pharmacology and Biopharmaceutics Review  
Clinical Pharmacology and Biopharmaceutics Review 125147/S-0000

115%

**FIGURE 16: Comparison of Mean (SE) PK Profiles between Non-Japanese (Studies 20030138 and 20030251) and Japanese Subjects (Study 20040192)**

**Subject Body Weights**

As body weight increased, the AUC showed a trend of decreasing for the fixed-dose regimen (Figure 17, right panel), whereas it showed a trend of increasing for the weight-based regimen (Figure 17, left panel). Furthermore, a ratio in AUCs across weight of 1.46 for a weight-based and 2.52 for a fixed dose suggests that the weight-based dosing regimen is expected to result in lower variability in Panitumumab exposure.

**FIGURE 17: Relationship between Body Weight and Simulated Steady State Exposure for Panitumumab Administered Once Every 2 Weeks (per sponsor's report # 104311)**

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# Met代谢数据检索及DDI预测的应用

- Case 5:** 抗肿瘤药物的代谢酶或转运体活性显著变化的信息检索
- Case 6:** 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢
- Case 7:** DDI预测计算的应用



# 药物相互作用的早期和持续评估至关重要

药物的相互作用(DDIS)会导致严重的副作用,并导致拒绝批准、严重的处方限制、药物退出市场,在极端情况下,会导致死亡。

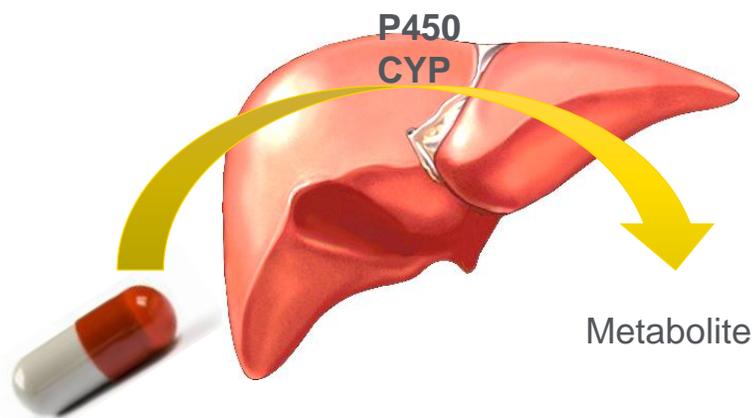
- 据FDA称,与DDI相关的药物不良反应报道数量正在上升。:
  - 越来越多的药物——以及更多的药物联用方案——被用于临床治疗,比以往任何时候都多
  - 1995年至2010年,成人配药比例增加了一倍,达到20.8%,成人配药比例增加了两倍,达到5.8%<sup>1</sup>
- 患者服用4种或更多药物后,药物不良反应率呈指数级增加
  - 2010年,13%的成人应为药物联用产生了严重副作用,这与多药治疗的治疗方案数量增加有关<sup>1</sup>



# 药物-药物相互作用可增加毒性或降低临床疗效。

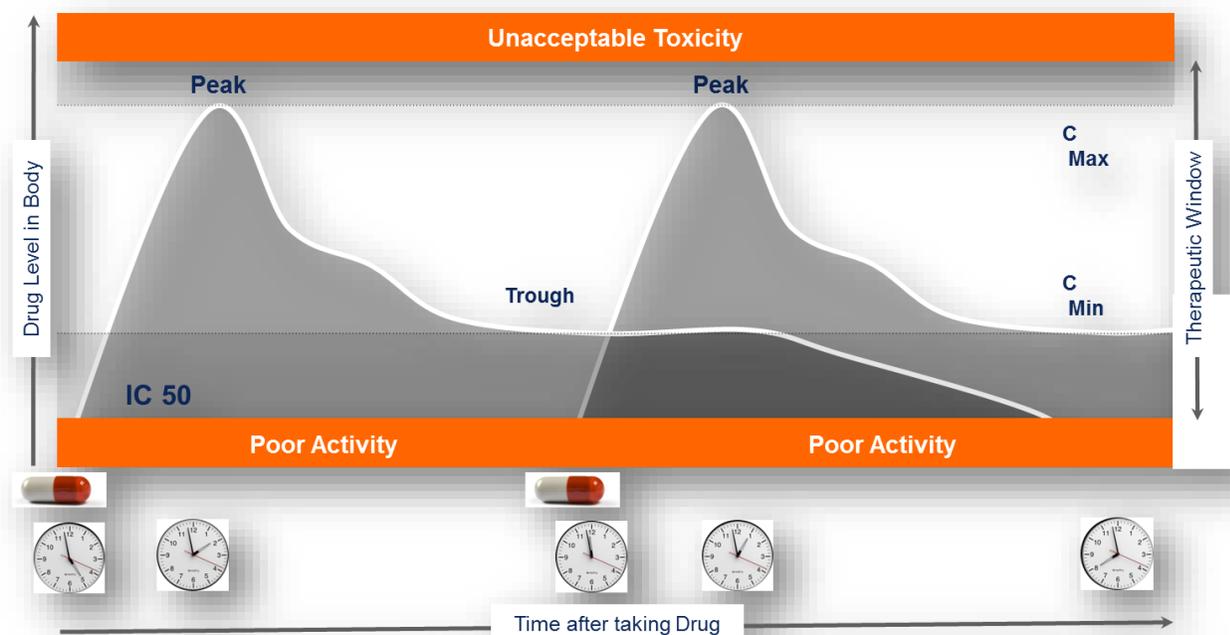
由AUC（曲线下面积）测量，增加/减少

药物代谢的主要机制（约占75%）是通过肝脏中的p450 CYP酶。



当伴随的药物\*抑制或诱导第二种药物的CYP的代谢时，可能会产生药物-药物的相互作用

伴随用药=同时服用两种或两种以上的药物



如，药物A口服，由CYP3A代谢

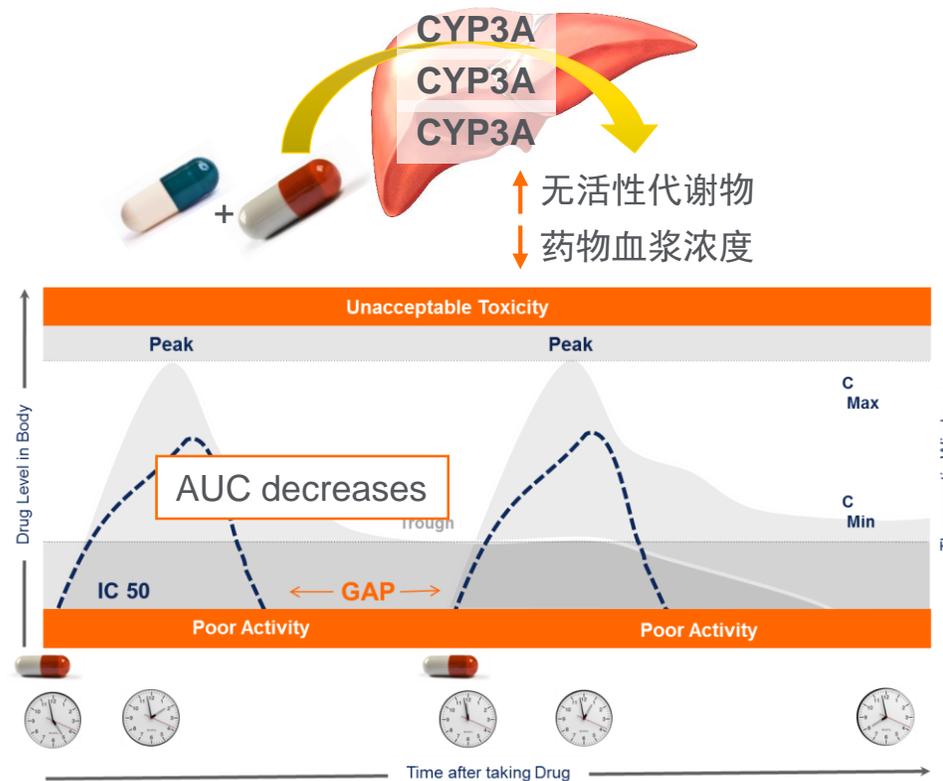
定时给药，使血浆浓度保持在足够高的水平，以最大限度地提高疗效，并降低到足以避免毒性

### 伴随药物抑制CYP酶的代谢



如,药物A由cyp3A代谢, 药物B抑制cyp3A的活性, 药物A不再以相同的速率代谢, 导致毒性浓度的累积

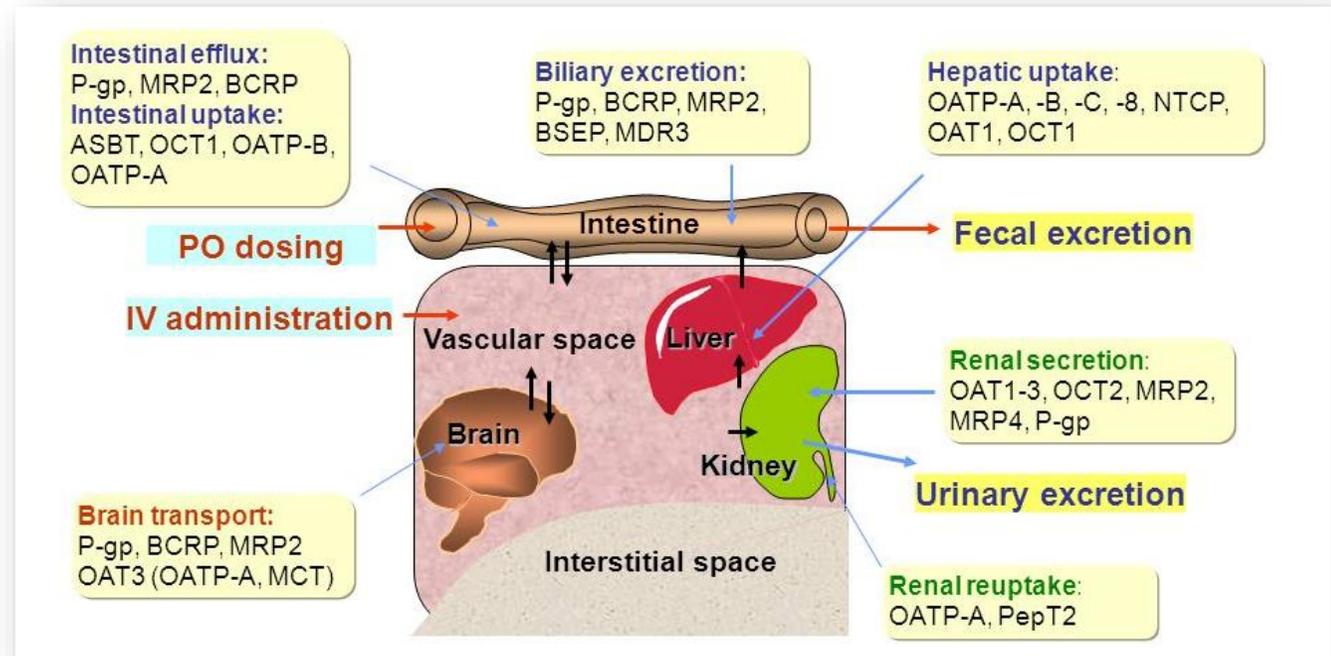
### 伴随药物诱导CYP酶的代谢



如,药物A由cyp3A代谢, 药物B诱导cyp3A的活性, 药物A不再以相同的速率代谢, 导致浓度降低, 疗效下降.

# DDI也通过联合用药抑制或诱导药物转运体发生

- 转运体在药物吸收和清除过程中常常与药物代谢酶协同工作。
  - 位于小肠、肝脏和肾脏，对药物吸收和清除至关重要
  - DDIS中常见的转运体包括P-糖蛋白1,多药耐药1 (P-gp/MDR1) 和BCRP (乳腺癌耐药蛋白)
- DMPK模块包含代谢酶和转运蛋白的综合信息



# DMPK 模块

为候选药物潜在的风险提供更完整的评估，辅助决策。

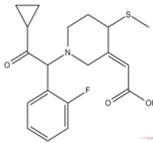
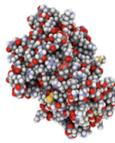
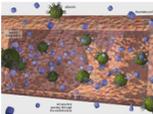
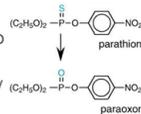
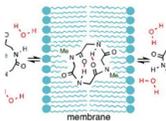
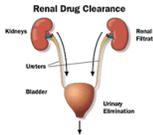
- 来自FDA和EMA批准文件包和部分文献中的综合性数据，以上市药物的经审批的标准数据为基础，帮助研发人员对候选药物药代动力学特性的有更深入理解。
- 最深入、最详细的代谢酶和转运体信息，使研发人员能够更深入地了解FDA和EMA审批上市药物的DDIs问题

## DDI 风险预测计算器(DDIRC)

- 快速辅助预测的基于代谢酶的DDI，辅助临床方案设计.
- 可以利用PK和MET模块中的数据来计算候选药物和上市药物之间的DDI风险。



# MET+PK参数直接定位对应信息

<p><b>Metabolites</b></p> <p>Created, when available</p> 	<p><b>CYPs</b></p> <p>Either involved in the metabolism or up/down regulated by the drug, quantitative and qualitative data</p> 	<p><b>Phase 2 Enzymes</b></p> 
<p><b>Transporters</b></p> <p>And drug effects on transporters</p> 	<p><b>In Vitro</b></p> <p><b>Dynamic parameters</b> such as CLint (Intrinsic Clearance) and Km (Michaelis Constant), Vmax (Maximum rate of reaction)</p> 	<p><b>DDI Studies</b></p> <p>Ratio of AUC, Clearance, etc. in presence of another drug.</p> 
<p>药物在检索时被分为: 底物, 诱导剂和抑制剂</p>		
<p><b>Absorption</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>% Absorbed</li> <li>Bioavailability</li> <li>Concentrations</li> <li>Fraction absorbed</li> <li>Time values</li> </ul> 	<p><b>Binding</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>Cell binding</li> <li>Protein binding</li> </ul> 	<p><b>Biotransformation</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>Enantiomeric ratio</li> <li>Metabolic ratio</li> <li>Metabolic stability</li> <li>Metabolic transformation</li> </ul> 
<p><b>Distribution</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>Accumulation</li> <li>AUC</li> <li>Permeation</li> <li>Steady state</li> <li>Time value</li> <li>Tissue distribution</li> <li>Volume of distribution</li> </ul> 	<p><b>Elimination</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>Clearance</li> <li>Excretion values</li> <li>Half life</li> <li>Rate constants</li> <li>Time</li> </ul> 	<p><b>Species</b></p> <p><b>Includes:</b></p> <ul style="list-style-type: none"> <li>Human</li> <li>Vertebrates</li> <li>Birds</li> <li>Fish</li> <li>Mammals</li> </ul> 

Ki	8.12 umol/L	Yes	FDA approval package document:	2009
Ki	37.3 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4-48.6 umol/L	Yes	FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	37.3 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009

既可以查看原始文献中的数据信息，也可以快速获取原文查看细节，帮助分析原始文献中数据细节

检索数据，来源于监管机构的官方档案

FDA Approval Package

Search this FDA Package

- Administrative documents
- Approval Letter
- Chemistry Review
- Clinical Pharmacology and Biopharmaceutics R...
  - 2009-01-30 PDF(2722k) Clinical Pharmacology and Biopharmaceut...
  - 2009-01-30 PDF(2612k) Clinical Pharmacology and Biopharmaceut...
  - 2009-01-30 PDF(4017k) Clinical Pharmacology and Biopharmaceut...
- Label
- Letter
- Medical/Clinical Review
- Medication Guide
- Other important information from FDA
- Pharmacology Review
- Review
- Statistical Review
- Summary Review

FDA Approval Package - Dronedarone Hydrochloride • Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review 022425/5-000 Part 02

Table 105: Apparent Ki values for Dronedarone and Amiodarone for bufuralol 1-hydroxylation (CYP2D6 activity determinant)

Microencapsulated Preparation	Apparent Ki Values (uM)	
	SR 335809	Amiodarone
HL 7-Jan-94	4.2	48.2
SD	0.3	4.5
HL 23-May-94	7.2	43.9
SD	0.8	5.0
HL 3-Mar-94	3.5	21.9
SD	0.3	2.3

Table 106: Apparent Ki values for Dronedarone for aldicarb oxidation (CYP3A4 activity determinant)

Microencapsulated Preparation	Apparent Ki Values (uM)
	HL 9-Jan-94
SD	2.9
HL 23-May-94	37.3
SD	3.2
HL 21-Feb-94	48.6
SD	3.3



# Case 5: 运用代谢酶和转运体模块进行数据检索

PharmaPendium®

Browse ▾ Search ▾ My tools ▾ |         Peng Wu    

Metabolizing Enz. & Transporters data search Clinical & preclinical data Reset all Search >

**Search Options** i

- Show all data for each selected FDA or EMA drug
- Show data only where selected drugs are studied together pairwise

\* Majority of the drug-drug interaction studies will have 2 drugs tested

**Drugs & Other Substances**

- + Add FDA/EMA drugs by drug class or drug name
- + Add FDA/EMA drugs by primary target or primary target class
- + Add drugs by indication
- + Add other substances

Note: for the current version, if you are searching for non-FDA or non-EMA approved drugs, we suggest that you search in both "Add FDA/EMA approved drugs by drug class or drug name" AND "Add other substances"

**Data type**

- + Add data types

**Enzyme/transporter name**

- + Add enzyme/transporter names

**Species**

- + Add species

**Sources**

- + Add sources

检索单个药物的代谢数据

检索有药物联用记录的数据

代谢酶/转运体数据精确定位

种属选择, 分类临床前, 临床数据

# 代谢酶和转运体—分类，整理

Add enzyme/transporter names

直接输入 'Cyp3A4 or MDR1'

Search on:

Search: Cyp3A4

- CYP3A
- CYP3A1
- CYP3A2
- CYP3A3
- CYP3A4
- CYP3A5
- CYP3A6
- CYP3A7
- CYP3A8
- CYP3A9
- CYP3A11

Search: MDR1

- MDR1
- MDR1a
- MDR1b
- MDR1(A893S)
- MDR1(S400N)
- MDR1(G1199A)

系统自动推荐相关选项，便于快速检索

# 抗肿瘤药物的代谢数据总览

PharmaPendium®

Browse Search My tools

Metabolizing Enz. & Transporters search results

39413 records from ME&T data: [Antineoplastics (39413)]

Show/hide columns Show drugs in... Save Export

Filters

Refine search: Apply Clear all

Drugs Routes of Administration Sources Data type Enzyme/transporter name Parent/Metabolite Test System Results (qualitative) Concomitant

Preclinical Data Clinical Data All Data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system	Species
1	Abarelix	Parent	Aberelix	Enzyme Substrate (in vitro)	Enzyme unspecified	Unreported	Human
2	Abarelix	Parent	Aberelix	Enzyme Substrate (in vivo)	Enzyme unspecified	Unreported	Human

Enzyme/transporter name

- Enzyme (26087)
- Transporter (10995)
- Unreported (2331)

Parent/Metabolite

- Enantiomer (10)
- Metabolite (2517)
- Parent (36886)

Results (qualitative)

- Ambiguous (657)
- No (11309)
- Yes (15056)
- Blank (Unreported) (12391)

# 抗肿瘤药物的代谢数据的深度提炼

PharmaPendium®

Browse Search My tools

Metabolizing Enz. & Transp

39413 records from ME&T data: [Ar]

Columns Show drugs in... Save Export

对批文中代谢数据的描述进行分类：如，在批准文件中写明某个参数（如AUC）有重大变化，则通过‘significant’筛选

Results (qualitative)

- Ambiguous (657)
- No (11309)
- Yes (15056)
  - Almost complete (1)
  - Complete (10)
  - Dominant (2)
  - Extensive (15)
  - Great (1)
  - Greatest (2)
  - High (6)
  - Large (1)
  - Less (60)
  - Likely (13)

Preclinical Data Clinical Data All Data

- Poor (58)
- Possible (5)
- Possibly (1)
- Potent (57)
- Predominant (49)
- Primarily (124)
- Significant (175)**
- Slight (95)
- Slow (1)
- Small (59)
- Some (2)
- Strong (100)
- Substantial (43)

ID	Drug	Observed	Data Type	Enzyme/Transporter	Test system	Species
1	Abarelix		Enzyme Substrate (in vitro)	Enzyme unspecified	Unreported	Human
2	Abarelix		Enzyme Substrate (in vitro)	Enzyme unspecified	Hepatocytes	Human
3	Abarelix		Enzyme Substrate (in vitro)	Enzyme unspecified	Unreported	Human
4	Abarelix		Enzyme Substrate (in vitro)	Enzyme unspecified	Unreported	Human
5	Abarelix		Enzyme Substrate (in vivo)	Enzyme unspecified	Not applicable	Human

# 抗肿瘤药物的代谢数据的一细节快速追踪

Preclinical Data Clinical Data All Data

ID	Drug	Route	Substance measured	Concomitants	Parameter	Value	Result (qualitative)	Source
26	Celecoxib						Yes, Significant	PharmaPendium Published European Journal of Pharr Sciences 2016; 81:137 Locate Article View Full S
27	Approval Package 209936/S-000 Part 02							
28	DDI研究的重要细节: Copanlisib主要是被CYP3A代谢, 强的CYP3A调节剂会对暴露量有显著影响。避免同时使用强CYP3A诱导剂, 并考虑替代性伴用药物, 降低CYP3A诱导的可能性。当Copanlisib与强CYP3A抑制剂药物联用时, 建议将剂量降低到45毫克。							

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management strategy?

Yes. Copanlisib is primary metabolized by CYP3A. Strong CYP3A modulators have significant effect on copanlisib exposures. Avoid concomitant use of strong CYP3A inducers and consider alternative concomitant medications with less potential for CYP3A induction. Dose reduction to 45 mg is recommended when coadministration of ALIQOPA with a strong CYP3A inhibitor.

There is a DDI potential between copanlisib and substrates of renal transporter MATE2-K. At recommended dosing regimen, copanlisib achieves C<sub>max</sub> around 1 μM that is about 10-fold of its IC<sub>50</sub> (0.09 μM) for MATE2-K. Metformin is a sensitive MATE2-K substrate used as a concomitant medicine in the pivotal trial to control hyperglycemia. It is also expected that

copanlisib与肾转运蛋白Mate2-K的底物之间存在DDI风险

substrates such as metformin, a post-marketing requirement will be issued.

ELSEVIER

# 抗肿瘤药物的代谢数据的一更多细节快速追踪

继续快速查找：copanlisib与肾转运蛋白Mate2-K相关的细节信息

FDA Approval

Label 209936/S-001

Effect of Copanlisib on CYP and Non-CYP Enzymes

Copanlisib is not an inhibitor of the metabolism of drugs that are substrates of the major CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or uridine diphosphate-glucuronosyltransferase isoforms (UGT) or dihydropyrimidine dehydrogenase (DPD) at therapeutic 60 mg dose plasma concentrations. Copanlisib is not an inducer of CYP1A2, CYP2B6 and CYP3A.

**Effect of Copanlisib on Drug Transporter Substrates**

Copanlisib is not an inhibitor of P-gp, BCRP, multi-drug resistance-associated protein (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1 at therapeutic 60 mg dose plasma concentrations.

Copanlisib is an inhibitor of **MATE2-K** (IC<sub>50</sub>: 0.09 μM). Based on the PK of copanlisib, inhibition may occur after copanlisib infusion at approved recommended dosage. The clinical significance of this potential inhibition on plasma concentrations of concomitantly administered drugs that are MATE2-K substrates is unknown.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been conducted with copanlisib.

Copanlisib did not cause genetic damage in *in vitro* or *in vivo* assays.

Fertility studies with copanlisib were not conducted; however, adverse findings in male and female reproductive systems were observed in the repeat dose toxicity studies. Findings in the male rats and/or dogs included effects on the testes (germinal epithelial degeneration, decreased weight, and/or tubular atrophy), epididymides (spermatic debris, decreased weight, and/or oligospermia/aspermia), and prostate (reduced

# Case 6: 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢

The screenshot displays the PharmaPendium web application interface. At the top, the PharmaPendium logo is on the left, and navigation links for 'Browse', 'Search', and 'My tools' are in the center. On the right, there are icons for home, search, and user profile, along with the name 'Peng Wu' and a notification bell. Below the navigation bar, the page title is 'Metabolizing Enz. & Transporters data search' with a sub-label 'Clinical & preclinical data'. A 'Reset all' button and a 'Search' button are on the right.

The main content area is divided into two columns. The left column, titled 'Search Options', contains two radio buttons: 'Show all data for each selected FDA or EMA drug' (selected) and 'Show data only where selected drugs are studied together pairwise'. Below this is a note: '\* Majority of the drug-drug interaction studies will have 2 drugs tested'. The right column, titled 'Data type', has a '+ Add data types' button highlighted with an orange box. Below it is the 'Enzyme/transporter name' section with a '+ Add enzyme/transporter names' button.

An 'Add data types' modal window is open in the foreground. It has a search bar 'Type data type to search' and a list of categories with checkboxes: 'Metabolizing Enzymes' (checked), 'Drug as Enzyme Inducer' (checked), 'Drug as Enzyme Inhibitor' (checked), 'Drug as Enzyme Substrate' (unchecked), 'Transporters' (unchecked), and 'Unspecified' (unchecked). A note at the bottom of the modal reads: 'Note: for the current version both "Add FDA/EMA approved" and "Add other substances" are required for drug-drug interaction studies'. The modal also has 'Cancel' and 'Done' buttons.

On the right side of the modal, under 'Search on:', there are two search results: 'Drug as Enzyme Inducer' and 'Drug as Enzyme Inhibitor', each with a close button (X).

The Elsevier logo is visible in the bottom left corner of the page.

# 检索CYP2D6有诱导或抑制作用的药物

PharmaPendium® Browse ▾ Search ▾ My tools ▾ |  Peng Wu    

Metabolizing Enz. & Transporters data search Clinical & preclinical data Reset all Search >

**Search Options** i

Show all data for each selected FDA or EMA drug  
 Show data only where selected drugs are studied together pairwise

\* Majority of the drug-drug interaction studies will have 2 drugs tested

**Drugs & Other Substances**

- + Add FDA/EMA drugs by drug class or drug name
- + Add FDA/EMA drugs by primary target or primary target class
- + Add drugs by indication
- + Add other substances

Note: for the current version, if you are searching for non-FDA or non-EMA approved drugs, we suggest that you search in both "Add FDA/EMA approved drugs by drug class or drug name" AND "Add other substances"

**Data type**

Drug as Enzyme Inducer ×

Drug as Enzyme Inhibitor ×

+ Add data types

**Enzyme/transporter name**

CYP2D6 ×

+ Add enzyme/transporter names

**Species**

+ Add species

**Sources**

+ Add sources

对信息的深度挖掘和整理，便于快速锁定对应结果

# Cyp2D6诱导剂或者抑制剂的检索结果

PharmaPendium®

Browse Search My tools

Metabolizing Enz. & Transporters search results

9764 records from ME&T data: [Drug as Enzyme Inducer (400) OR Drug as Enzyme Inhibitor (9364)] AND [CYP2D6 (9764)]

Filters

Refine search:

Apply Clear all

Drugs

Routes of Administration

Sources

Data type

Enzyme/transporter

Parent/Metabolite

Test System

Results (qualitative)

Preclinical Data Clinical Data All Data

ID

Substance Studied

Bergapten

Bergapten

Abacavir

Abacavir sulfate

Abacavir sulfate

Abacavir

Abacavir

Abacavir

Enzyme Inhibitor (In CYP2D6 Unreported Human

Show drugs in

Deselect all

Export All drugs in Excel file (.xls)

Show the filtered drugs in other modules. Based on your filtering.

Selected: 747

- 5-Methoxypsoralen
- Abacavir Sulfate
- Abemaciclib
- Abiraterone Acetate
- Acamprosate Calcium

> Show in Pharmacokinetic Data

> Show in Drug Safety Data

> Show in FAERS Data

> Show in Efficacy Data

> Show in Activity Data

vitro)

ELSEVIER

当原文中，对抑制性或者诱导性有定性描述时，会被归类到筛选器中

# Cyp2D6诱导剂或者抑制剂筛选结果

导出归档对CYP2D6有较严重或诱导的药物数据

Metabolizing Enz. & Transporters search results

68 records from ME&T data: [Drug as Enzyme Inducer (0) OR Drug as Enzyme Inhibitor (68)] AND [CYP2D6 (68)] AND [Yes, High (1) OR Yes, Major (2) OR Yes, Modest (22) OR Yes, Potent (10) OR Yes, Significant (11) OR Yes, Strong (22)]

Show/hide columns > Show drugs in... > Save Export

Filters

Refine search:

Apply Clear all

Drugs

Routes of Administration

Sources

Data type

Enzyme/transporter name

Parent/Metabolite

Test System

Results (qualitative)

> Yes (68)

Preclinical Data Clinical Data All Data

原文中标注有强烈，抑制或诱导效果，便捷快速分类

ID	Drug	Intants	Parameter	Value	Result (qualitative)	Source	Year
1	Abiraterone Acetate		Activity (no value)		Yes, Strong	FDA approval package document: Pharmacology Review (Page:11) View Full Study PDF 571k	2011
2	Abiraterone Acetate		unspecified		Yes, Strong	FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:40) View Full Study PDF 598k	2010
3	Abiraterone Acetate		Ki	0.39 $\mu$ M	Yes, Potent	FDA approval package document:	2010
4	Abiraterone Acetate						
5	Abiraterone Acetate						
6	Abiraterone Acetate						

Hide Filters

**Study # 400379** was performed to determine the potential for inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C8 was not assessed) by abiraterone acetate (0.1 -10  $\mu$ M) and abiraterone (0.1 -10  $\mu$ M).

- Abiraterone (CB7598) was a not an inhibitor for human CYP2A6 and CYP2E1 while it was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5 and a potent inhibitor of CYP1A2 and CYP2D6 over the concentrations tested.
- Abiraterone acetate (CB7630) exhibited no inhibition towards CYP2A6, but showed a moderate inhibition towards CYP2E1, CYP2C9 and CYP3A4/5 and a potent inhibition towards CYP1A2 and CYP2C19 over the concentration range tested

Clinical Pharmacology and Biopharmaceutics Review (Page:39)

# 在研药物Cyp2D6为基础的DDI预测

PharmaPendium®

Browse Search My tools

Peng Wu

## Proprietary Victim Drug

### Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

\*Compound name: test 1

Hepatic Metabolism

- User Defined
- Predicted

Enzyme(s)

CYP2D6

Select

kdeg (min-1)

0.000226

fmE

0.9

假设在研药物为‘受害药’，主要被CYP2D6代谢

代谢程度达到90%

Predict interactions

在预测出来的DDI结果中，导出excel表格，结合之前的结果，快速对比筛选，CYP2D6的抑制剂或者激动剂与在研药物可能存在DDI风险的结果

PharmaPendium®

Browse Search My tools

Help on charts Save Export

DDI Prediction

198 records from DDI Risk Calculator: victim: test 1

Results

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min.	Max.	Mean	SD	Med.
1	(+)-Citalopram 147856 Antidepressant Dev: + Drug Type: Approved	Multiple			132	1.006	1.041	1.014	0.009	1.011
2	(+)-Propoxyphene 91412 Analgesic: narcotic/opiate Dev: + Drug Type: Approved	Multiple			4	2.509	6.835	4.677	2.157	4.682
3	(-)-Omeprazole 162827 Antilucerative Proton pump inhibitor Dev: - Drug Type: Approved	Multiple			88	1.005	1.09	1.036	0.027	1.022
4	Acamprosate 241873	Multiple			126	1.01	1.238	1.089	0.06	1.077



# 哪些Cyp2D6的抑制剂或诱导剂于在研药物存在DDI风险

Victim	Perpetrator1	Dose/unit	AUC Ratio			Count	Color	AUC rati
test 1 (+)-Propoxyphene	-Analgesic: narcotic/opiate-	0.6 g	6.834	6.835	6.834	2		
test 1 Budipine	-Antiparkinsonian-	0.01 g	5.11	5.11	5.11	1		
test 1 Cimetidine	-Antihistaminic-Antiulcerative-	0.3 g	5.385	6.672	6.052	180		
test 1 Cimetidine	-Antihistaminic-Antiulcerative-	0.8 g	7.844	8.601	8.276	1		
test 1 Fluvoxamine	-Antidepressant-	0.05 g	5.423	6.34	5.863	1		
test 1 Fluvoxamine	-Antidepressant-	0.1 g	6.058	8.46	7.362	36		
test 1 Mibefradil	-Antianginal-Antihypertensive-Calcium channel blocker-	0.043 g	9.974	9.992	9.983	17		
test 1 Mibefradil	-Antianginal-Antihypertensive-Calcium channel blocker-	0.1 g	9.992	9.998	9.995	17		
test 1 Mibefradil	-Antianginal-Antihypertensive-Calcium channel blocker-	0.15 g	9.995	9.999	9.997	17		
test 1 Mibefradil	-Antianginal-Antihypertensive-Calcium channel blocker-	0.25 g	9.998	9.999	9.999	17		
test 1 Nilotinib	-Antineoplastic-	0.8 g	5.625	5.762	5.694	2		
test 1 Nilotinib	-Antineoplastic-	1.2 g	6.454	6.537	6.496	2		
test 1 Paroxetine	-Antidepressant-	0.02 g	7.983	9.845	9.266	126		
test 1 Paroxetine	-Antidepressant-	0.03 g	9.107	9.913	9.634	42		

高风险的侵害药列表

Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone (CB7598)	Enzyme Inhibitor (in vitro)	CYP2D6	Unreported	Human	0.1 -10 uM
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Unreported	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Unreported	Human	0.1 -10 uM
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Parent	Abiraterone Acetate	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Liver, microsomes	Human	Unreported
<a href="#">Abiraterone Acetate</a>	Metabolite	Abiraterone	Enzyme Inhibitor (in vitro)	CYP2D6	Hepatocytes	Human	0.1-10 uM
<a href="#">Asenapine Maleate</a>	Parent	Asenapine	Enzyme Inhibitor (in vitro)	CYP2D6	Unreported	Human	Unreported
<a href="#">Buprenorphine</a>	Parent	Buprenorphine	Enzyme Inhibitor (in vitro)	CYP2D6	Enzyme, recombinant	Human	Unreported
<a href="#">Cinacalcet Hydrochloride</a>	Parent	Cinacalcet hydrochloride	Enzyme Inhibitor (in vitro)	CYP2D6	Unreported	Human	Unreported

CYP2D6抑制剂或者诱导剂



# Met代谢数据检索及DDI预测的应用

**Case 5:** 抗肿瘤药物的代谢酶或转运体活性显著变化的信息检索

**Case 6:** 哪些药物可以与我的药物相互作用，并且由CYP2D6代谢

**Case 7:** DDI预测计算的应用



# 在药物的研发过程中会持续的评估DDI的情况

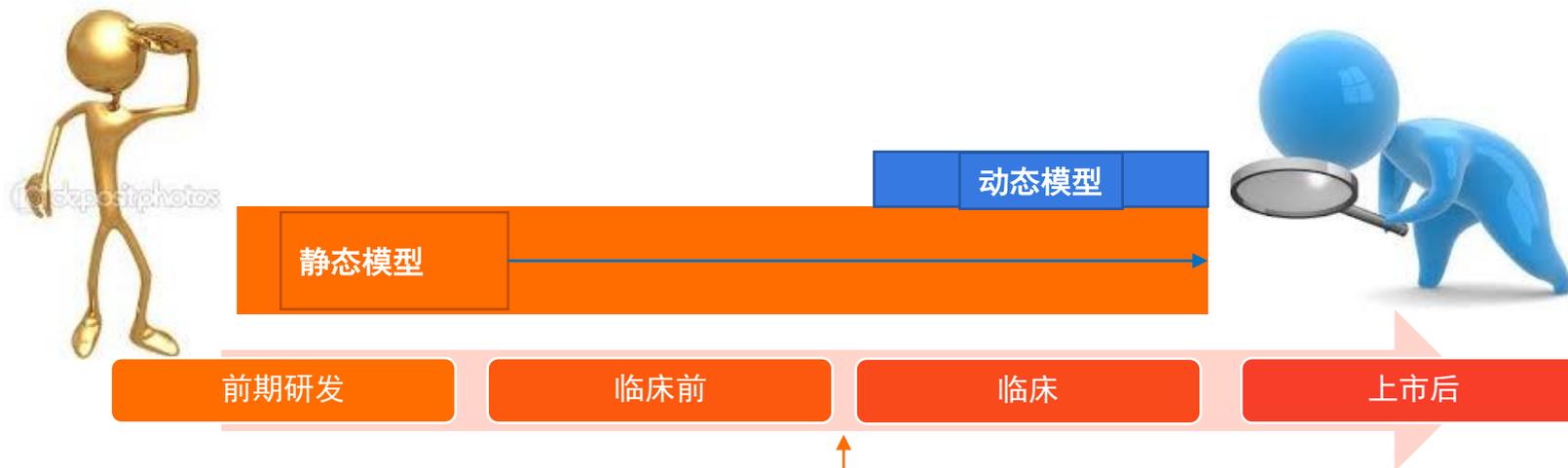
FDA建议在DDI评估时，应当逐步的，以模型为基础制定评估方案

## 早起开发阶段中: 更完善的评估策略

- 静态统计模型(e.g., **DDI 风险计算器**) 总览可能存在的DDIs风险
- DDIRC 模块中已有的底层数据 (如文献报道的数据), 帮助更早进行DDI预测. 后期获得实验数据以后, 还可以进行更精确的计算。

## 后期研发阶段: 更细致的评估

- 动态和静态模型中的信息是免费的, 用于评估特定药物之间的DDI风险, 并确定哪些药物可以与临床研究中的候选药物一起使用
- 机械动力学建模 (PBPK建模-例如, SimCYP) 需要大量输入数据和每个相互作用药物的PBPK模型的可用性



DDI risk calculated (e.g., using a Mechanistic Static model (DDIRC)):

- 可用于对豁免临床试验评估DDI风险提供证据
- 可以为临床前, 临床实验的决策提供证据

# PharmaPendium DDI 风险预测计算器(DDIRC)

预测潜在的DDI风险（受害药或者侵害药）

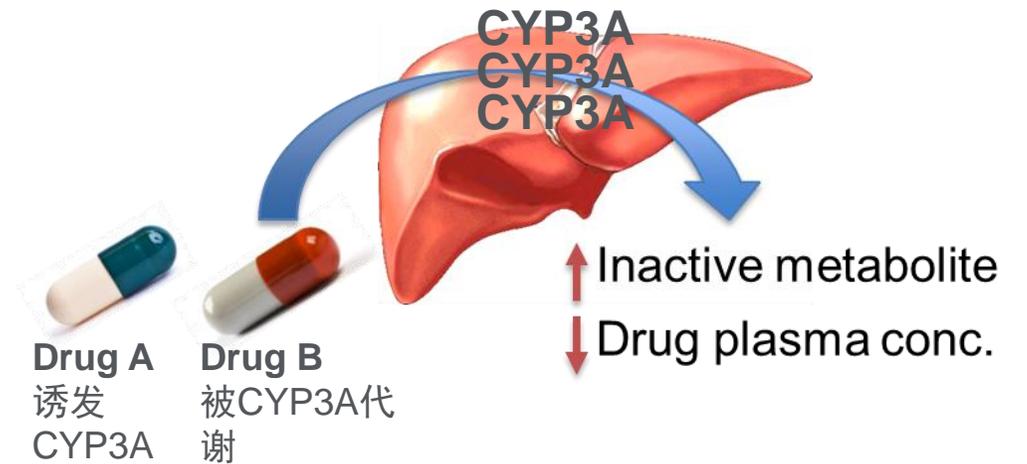
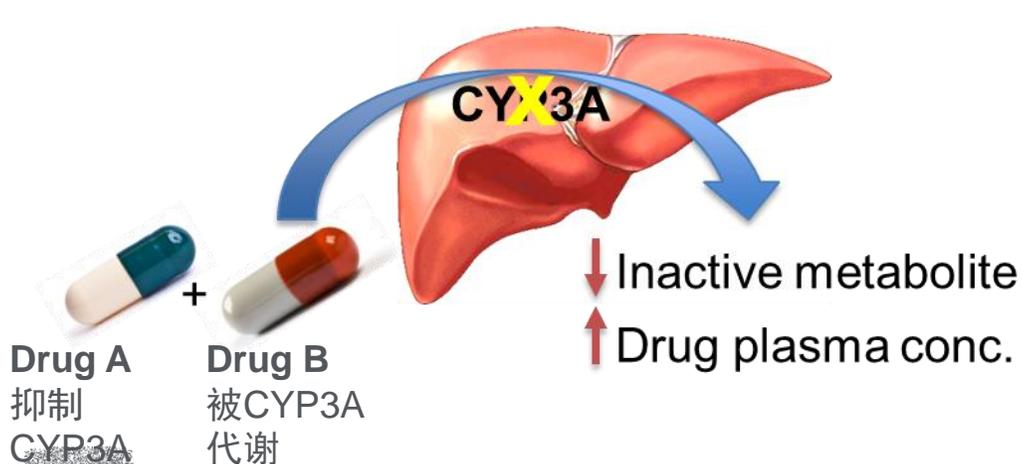
- 在整个药物的开发阶段（临川前，临床）都需要考虑DDI潜在的风险
  - 已上市的药物对于在研药物的影响
  - 在研药物对已上市药物的影响

侵害药：会影响其他药物的药代动力学

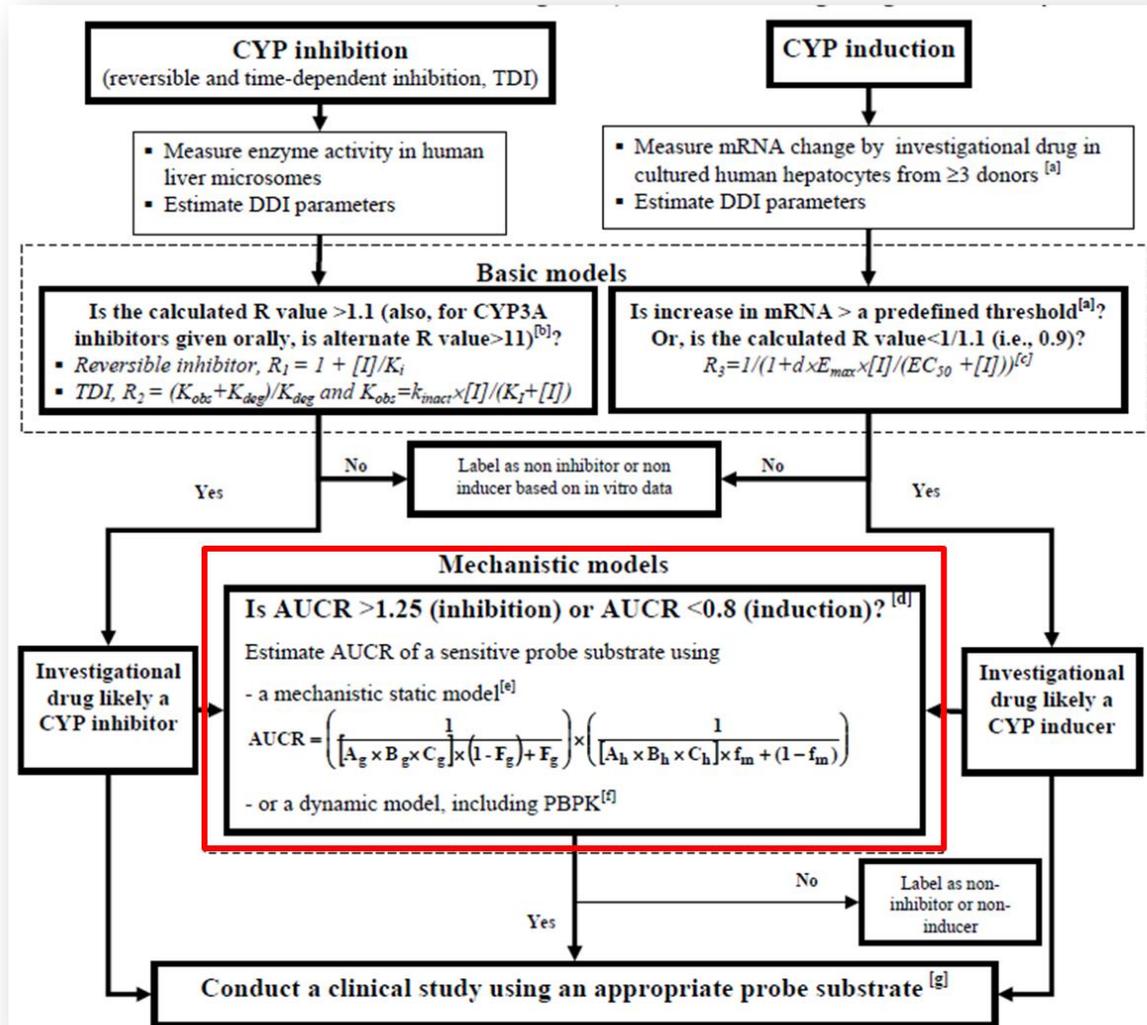
受害药：由于与其他药物的相互作用，而影响了自身的药代动力学

Drug A 是侵害药

Drug B 是受害药



# DDIRC 是依据FDA的指南设计的



## Guidance for Industry Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations February 2012

“本指南反映了监管机构的观点，即在药物开发过程中，作为对药物安全性和有效性的充分评估的一部分，应确定研究性新药和其他药物之间的药代动力学相互作用。”

# DDIRC 辅助 DDI 研究及临床实验决策

- 根据FDA的指南，新药相互作用研究的总体目标是确定：
  - 在研药物本身是否可能由于过多的药物相互作用问题，导致其在与其他药联用时需要改变剂量使用，或者联用药物需要改变剂量
  - 是否有任何相互作用需要额外的治疗监测
  - 是否应该有药物联用的限制使用措施，如果减低剂量仍然不能降低风险.

No DDI predicted with sensitive substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6

Significant DDI predicted with some sensitive substrates of CYP3A4



CYP3A4 substrates **prohibited** from clinical trials

## Real example of how DDIRC impacted clinical trial design

	Sensitive substrate	AUC increase
<b>CYP1A2</b>	Caffeine	×1
<b>CYP2B6</b>	Bupropion	×1
<b>CYP2C8</b>	Repaglinide	×1
<b>CYP2C9</b>	Celecoxib	×1
<b>CYP2C19</b>	Omeprazole	×1
<b>CYP2D6</b>	Dextromethorphan	×1
<b>CYP3A4/5</b>	Lovastatin	×5.5
	Nisoldipine	×4.5
	Buspirone	×4.1
	Sildenafil	×2.2
	Saquinavir	×2
	Midazolam	×1.9
	Felodipine	×1.8
	Alfentanil	×1.6
	Triazolam	×1.6
	Maraviroc	×1.3
	Aprepitant	×1
Darunavir	×1	

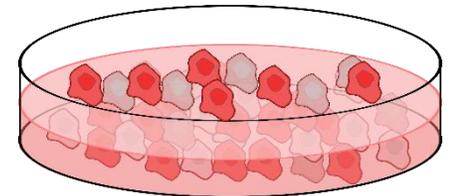
# How does the DDI Risk Calculator work?

It uses a **Mechanistic Approach**, extrapolating *In vitro* data on drug metabolism to humans in order to predict drug-drug interactions (called **In vitro In vivo extrapolation** or **IVIVE**)

## Some background:

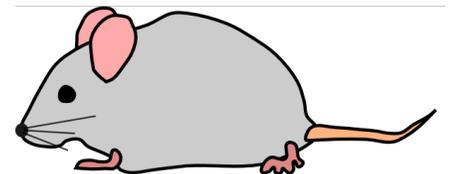
*In vitro* refers to techniques used to perform a given procedure outside a living organism – e.g., experiments performed in a test tube or cell culture

*In vivo* refers to experimentation using a whole living organism – e.g., experiments performed in an animal model



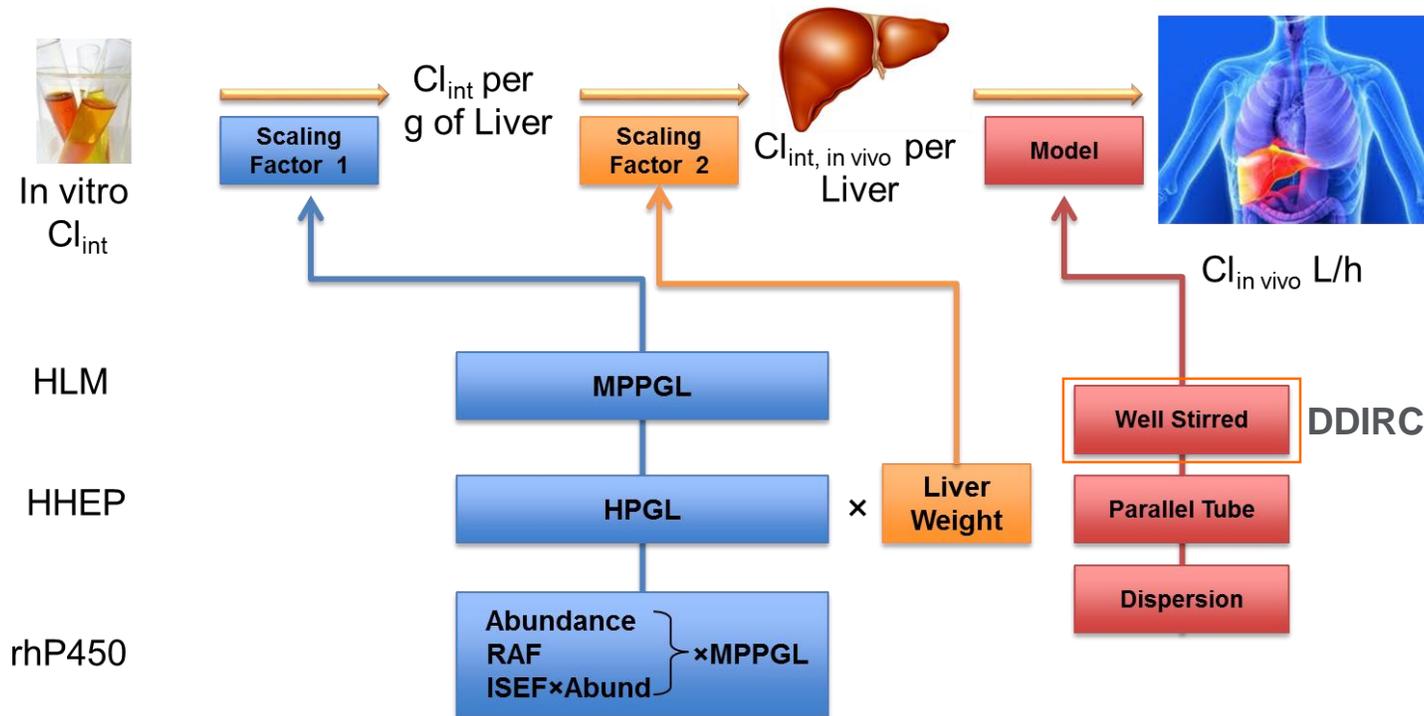
In vitro

In vivo



# DDI计算器如何计算

运用不同的体外数据来推测体内的可能出现的结果



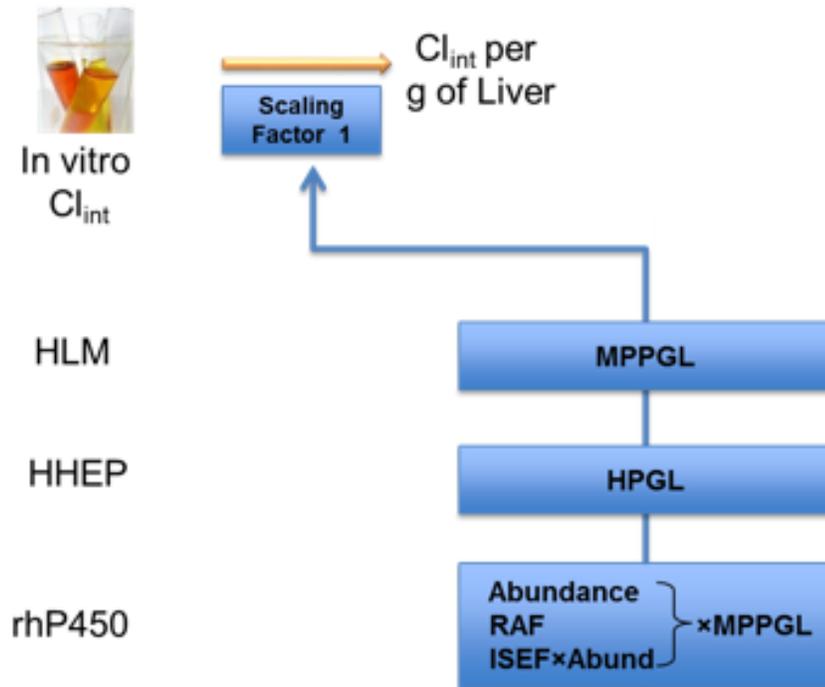
## Predicting hepatic clearance

*In vitro* clearance ( $Cl_{int}$ ) values are determined ( $K_m$  and  $V_{max}$ )

- **Scaling Factor 1** extrapolates this data to clearance per gram of liver
- This number is multiplied by the liver weight (**Scaling Factor 2**) to extrapolate the data to clearance in the liver ( $Cl_{int, in vivo}$ )
- The '**Well Stirred**' model is applied to determine level of hepatic clearance in the body ( $Cl_{in vivo}/L/h$ )

# 数据模型的应用

## Scaling Factor 1



Different scaling factors are applied depending on the *In vitro* system used

药物代谢的体外动力学研究（测量 $k_m$ 和 $v_{max}$ ）的数据用于评估肝药物清除率

There are different *In vitro* approaches using different human derived materials:

- Human Liver microsomes (HLM)
- Human hepatocytes (HHEP)
- Recombinant enzymes (rhP450) using different cell systems:
  - Baculovirus
  - Lymphoblastoid
  - E. Coli
  - Yeast

# 数据模型的应用

## Scaling Factor 1 (continued)

Results from recombinant enzyme experiments are scaled up to human liver microsomes (HLM) using values from the **DDI Risk Calculator** before they are extrapolated to *In vivo* clearance.

The user can choose between 3 different scaling factors:

- Abundance
- Relative Activity Factor (RAF)
- Intersystem Extrapolation Factor (ISEF) methods

## Proprietary Victim Drug

### Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

\*Compound name:

Hepatic Metabolism

User Defined  Predicted

HLM  hRecombinant

ISEF  
 RAF  
 Abundance

baculovirus  
 Lymphoblastoid  
 E. Coli  
 Yeast

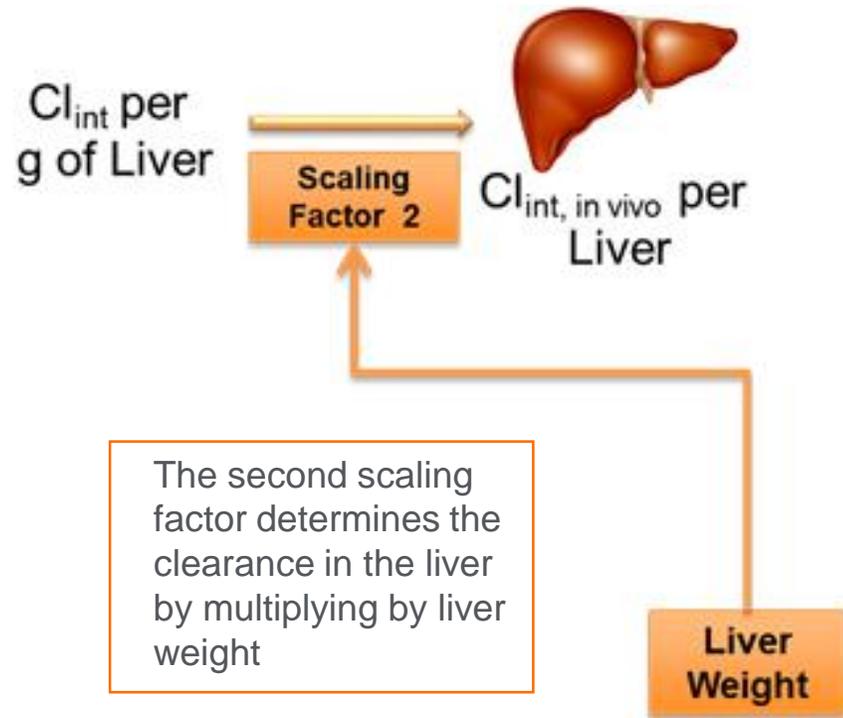
fm(E) Prediction

In Vitro enzyme contribution : fm(E)vitro

Enzyme(s)	kdeg (min <sup>-1</sup> )	Clint (μl/min/pmol)	Km (μM)	Vmax (pmol/min/pmol)	[C]prot (g/l)	ISEF	Abund. (pmol/mg)
CYP1A2	0.0003					0.9	48.8
Select							

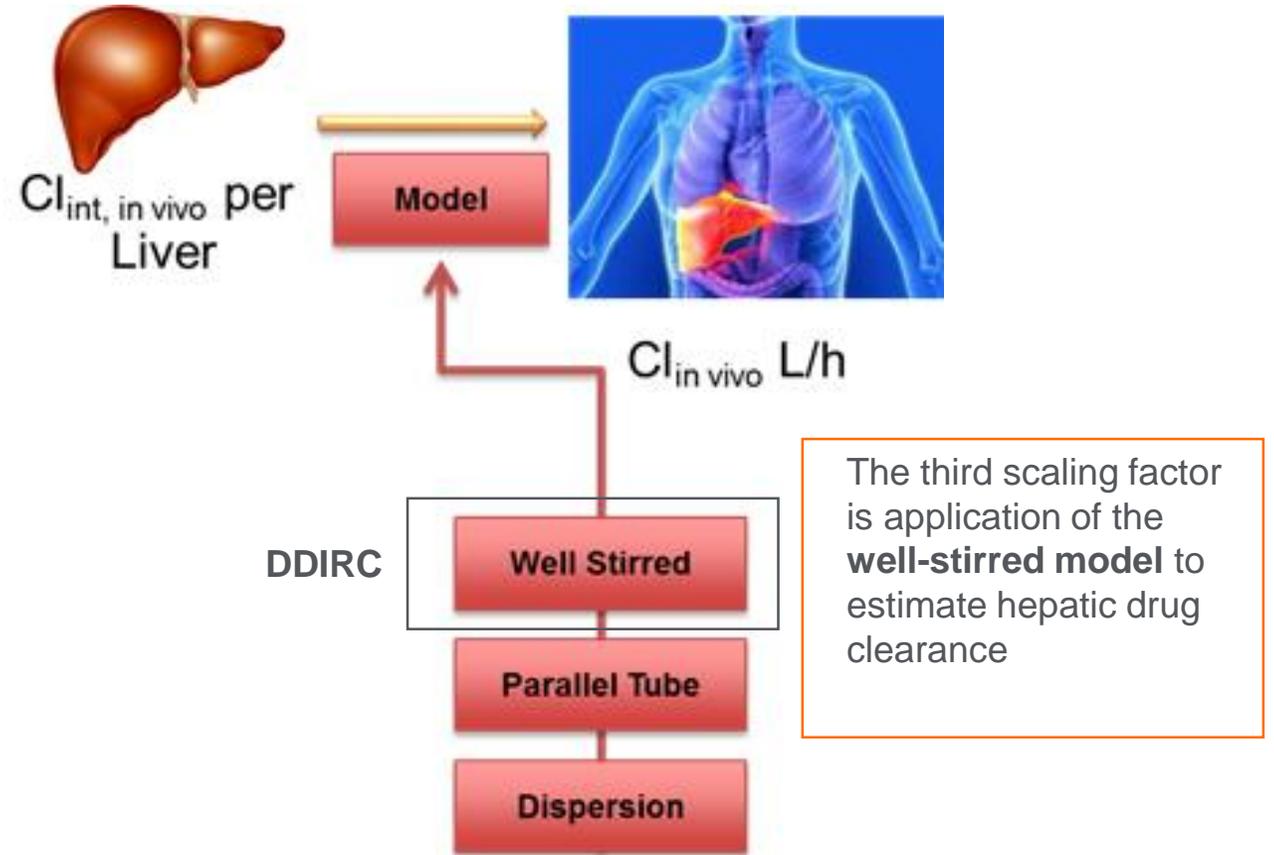
# 数据模型的应用

## Scaling Factor 2

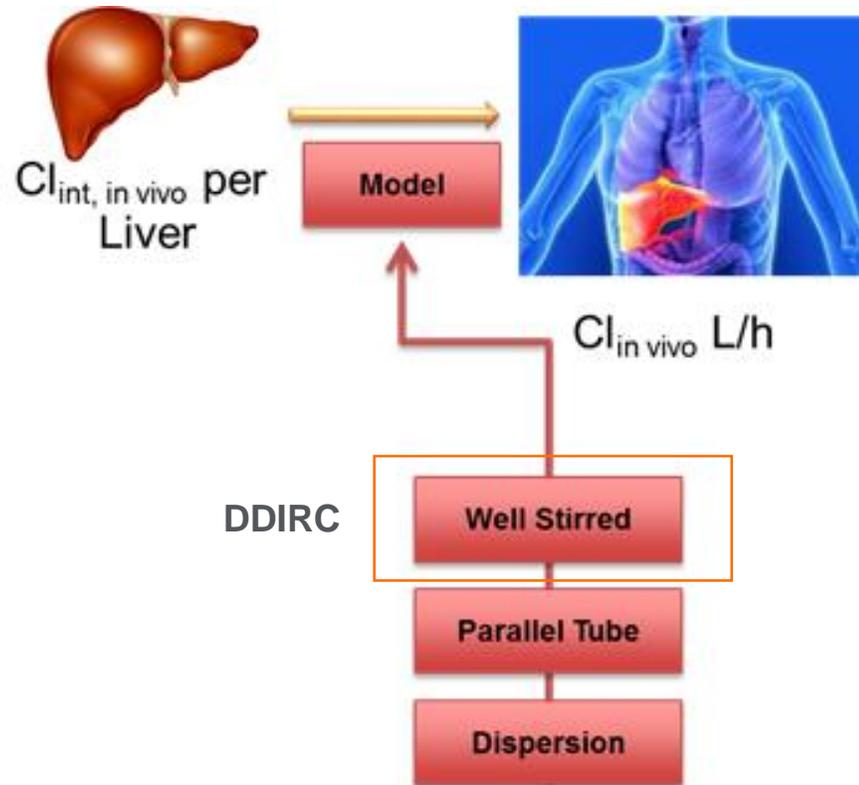


# 数据模型的应用

## Scaling Factor 3



# DDIRC 对于肝清除率计算使用 Well-Stirred模型



**Well-stirred model(充分混合模型):**肝脏是一个单独的器官，假设药物浓度在整个器官中是相等的

**Parallel-tube model(平行管模型):**肝脏是一组相同的平行排列的管子，沿着血流路径在肝脏中产生药物浓度梯度

**Dispersion model(弥散模型):**肝脏是一个内部血液分散的网状器官。计算出药物浓度介于充分搅拌和分散模型之间

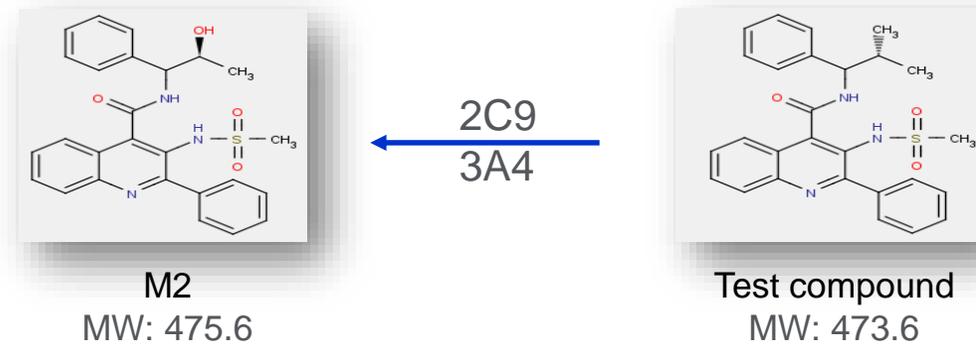
充分混合模型是估计肝脏清除率最常用的模型。

➤ 但是会导致比较轻微的过度评估DDIs风险

# DDIRC Demo: Test compound as a victim

# 测试化合物为受害药物

- 预测测试化合物与侵害药（M2）之间的相互作用关系
- 预测测试化合物与抗心律失常药物的作用关系



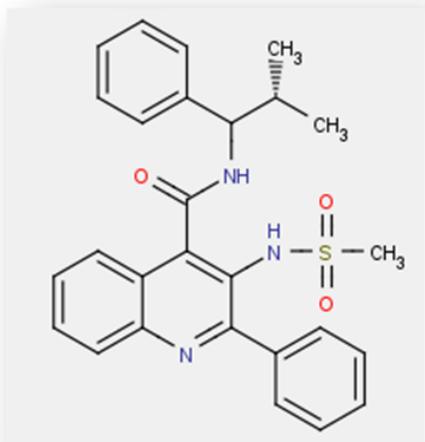
## 重组固有清除率（Recombinant Intrinsic Clearance）

细胞系统（Cell system: Insect cells Infected with Baculovirus）

• **M1:** 3A4  $K_m=8.6\mu\text{M}$   $V_{max}=0.87$  pmol/min/pmol [C] prot=0.5 mg/ml

• **M2:** 3A4  $K_m=32\mu\text{M}$   $V_{max}=3$  pmol/min/pmol [C] prot=0.5 mg/ml  
2C9  $K_m=4\mu\text{M}$   $V_{max}=0.1$  pmol/min/pmol [C] prot=0.5 mg/ml

# 测试化合物的物化性质以及血浆结合率



## ➤ Binding:

- fu (plasma): 0.4-0.5
- Rb: 0.55 Default

## ➤ Physchem

Molecular weight:	459.2
Total weight:	459.2
PSA:	88.16
pKa (pH 7.4):	7.66
logP:	4.28
logD (pH 7.4):	4.11
HBA (pH 7.4):	4
HBD (pH 7.4):	2
Rotatable bond count:	6
Polarizability (pH 7.4):	53.03
Refractivity:	128.96
Matching Lipinski rules:	4
Matching Veber rules:	2

Values powered by JChem from [ChemAxon](#)

# Predict DDIs with the proprietary drug as a victim

## DDI risk calculator

### Predict DDI: Proprietary Victim Drug

Start

Predict all interactions of your proprietary victim drug vs all perpetrators in DDI Knowledgebase

### Predict DDI: Proprietary Perpetrator Drug

Start

Predict all interactions of your proprietary perpetrator drug vs all victim drugs in DDI Knowledgebase

# 通过输入数据来预测FmE

## Proprietary Victim Drug

### Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

\*Compound name:

Hepatic Metabolism

- User Defined  
 Predicted
- HLM  
 hRecombinant
- ISEF  
 RAF  
 Abundance
- baculovirus  
 Lymphoblastoid  
 E. Coli  
 Yeast

1

fm(E) Prediction

In Vitro enzyme contribution : fm(E)vitro

Enzyme(s)

CYP3A4

CYP2C9

Select

kdeg (min-1)

0.00032

0.00011

Clint (µl/min/pmol)

2

Km (µM)

3

Vmax (pmol/min/pmol)

4

[C]prot (g/l)

ISEF

0.32

0.86

Abund. (pmol/mg)

173

69.6

Hepatic Fraction fh

- User Defined  
 Predicted

fh

fh prediction

Cl

Cl non hepatic

ClH

fup

Qh

1

1.61

Predict fh

6

Note: In addition to "Cl non hepatic" and "fup" values, please make sure that the values for Clint, [C] prot, and the microsomal binding values (fu(mic) and Prot. Conc.) are entered. Only then you will be able to complete the prediction of fh.

Microsomal binding

fu(mic)

Prot. conc.:

g/L

Calculate fu(mic)

5

Predict Fme

7

fu(mic) Calculation

Pka

Prot. conc.

g/L

g/L

Hallifax/Houston

Austin

Calculate

1. Select test system
2. 输入 Km (米氏常数)
3. 输入 Vmax (酶促反应最大速率)
4. 输入 [C]prot
5. 计算 fu(mic) – 输入 Pka, Prot conc, logP
6. 计算 hepatic fraction(fh) – 输入 Cl non-hepatic 和 fup
7. 预测 fmE

# 侵害药物FmE预测

## Proprietary Victim Drug

Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

\*Compound name:

Hepatic Metabolism

User Defined  
 Predicted

HLM  
 hRecombinant

ISEF  
 RAF  
 Abundance

baculovirus  
 Lymphoblastoid  
 E. Coli  
 Yeast

Enzyme(s)

CYP3A4  
CYP2C9

kdeg (min-1)

0.00032  
0.00011

fmE

0.78  
0.22

fm(E) Prediction

In Vitro enzyme contribution : fm(E)vitro

Enzyme(s)

CYP3A4  
CYP2C9  
Select

kdeg (min-1)

0.00032  
0.00011

Clint (µl/min/pmol)

0.09375  
0.025

Km (µM)

32  
4

Vmax (pmol/min/pmol)

3  
0.1

[C]prot (g/l)

0.5  
0.5

ISEF

0.32  
0.86

Abund. (pmol/mg)

173  
69.6

Hepatic Fraction fh

User Defined  
 Predicted

fh 1.00

fh prediction

Cl 17.070 L/h  
 Cl non hepatic 0 L/h  
 ClH 17.070 L/h  
 fup 0.4  
 Qh 1.61 L/min

Predict fh

Note: In addition to "Cl non hepatic" and "fup" values, please will be able to complete the prediction of fh.

Microsomal binding

fu(mic): 0.399

Prot. conc.: 0.5 g/L

Calculate fu(mic)

fu(mic) Calculation

Pka 7.66  
Prot. conc. 0.5 g/L  
LogP 4.28

Calculate

也可以计算侵害药物的相关数据(in this example, we will not change the default parameters)

1. 选择体系
2. 输入 Km
3. 输入 Vmax
4. 输入 [C]prot
5. 计算 fu(mic) – 输入 Pka, Prot conc, logP
6. 计算 hepatic fraction(fh) – 输入 Cl non-hepatic 和 fup
7. 预测 fmE (如, 通过Cyp3A4代谢)

Exclusively hepatic metabolism = worst case scenario

# Modify intestinal metabolism data (if required)

We have no data on gut metabolism (肠代谢), so leave Fg at 1

Intestinal Metabolism

User Defined  
 Predicted

**i** Fg

**i** Intestine inhibition : Estimation of Fg'/Fg ratio

**i**  Model Predicted  
**i** Qg  L/h  
**i**  Maximal Inhibition (Fg'/Fg)=1/Fg

fm(E)g Prediction

Enzyme(s)	kdeg (min-1) <b>i</b>	Clint (μl/min/pmol)	[C]prot (g/l)	Abund. (pmol/gut)
CYP3A4	<input type="text" value="0.0005"/> <b>i</b>	<input type="text" value="0.09375"/>	<input type="text" value="0.5"/>	<input type="text" value="62000"/>

**i** fug

 **Predict interactions**

# 257 侵害药结构 – 点击蓝色链接都有细节

DDI Prediction 257 records from DDI Risk Calculator: *Victim: Test*

Results **1** **2** **3** **4** **5** Help on charts > Save Export Export data for more info

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min.	Max.	Mean	SD	Med.	5-95th Perc.
1	<a href="#">(+)-Propoxyphene 91412</a> Analgesic: narcotic/opiate Dev.: + Drug Type: Approved	Multiple			4	1.061	1.554	1.308			
2	<a href="#">(+)-Warfarin 162426</a> Antithrombotic Dev.: + Drug Type: Experimental/Investigation	0.007 g			1	1.075	1.075	1.075			
3	<a href="#">(-)-Omeprazole 162827</a> Antiulcerative Proton pump inhibitor Dev.: - Drug Type: Approved	Multiple			88	1.022	1.078	1.051			
4	<a href="#">(-)-Warfarin 161583</a> Antithrombotic Dev.: - Drug Type: Experimental/Investigation	0.007 g			5	1.033	1.142	1.094	0.035	1.096	1.045-1.135
5	<a href="#">AMG 487 628746</a> Dev.: - Drug Type: Unspecified	Multiple			3						
6	<a href="#">Acamprosate 241873</a> Drug Type: Approved	Multiple			2646						
7	<a href="#">Acetaminophen 99468</a> Analgesic: non narcotic	Multiple			72	4.048	4.134	4.088	0.025	4.09	4.053-4.129

**Bar chart information**

The bar chart displayed in the DDI table is a color coded graphical overview of the risk assessment.

Color codes represent AUC/AUC ratio ranges corresponding to the FDA classification [1] of CYP inhibitor and inducer potency. The size of each colored segment in the bar represents the percentage of the total number of calculated AUC ratios (for a given victim/perpetrator couple) that falls into one of the following categories:

Category	AUC ratio range		Colour	
Risk(Induction)		AUC ratio <	0.8	
No risk	0.8	≤ AUC ratio <	1.25	
Low risk	1.25	≤ AUC ratio <	2	
Medium risk	2	≤ AUC ratio <	5	
High risk	5	≤ AUC ratio		

[1] <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...>

**Dose effect**

Dose	AUC Ratio	Count	Min	Max.	Mean	SD	Med.	5-95th Perc.
0.025 g		1	2.82	2.82	2.82	0.0	2.82	2.82-2.82
0.1 g		1	7.778	7.778	7.778	0.0	7.778	7.778-7.778
0.25 g		1	18.223	18.223	18.223	0.0	18.223	18.223-18.223

- 侵害药信息(物化性质)
- 剂量(Dose 可以查看不同剂量下的AUC)
- MBI (indicated here if it's mechanism-based inhibition)
- AUC Ratio (不同颜色表示程度不同)
- Count (细节在下一页)
- Min, max, mean, SD, median and 5-95<sup>th</sup> percentile AUC values

# 'count' 选项的细节

蓝色连接会有更多细节

DDI Results details Export

Victim: Test		Perpetrator: (-)-Omeprazole																	
AUCi/AUC	F'g/Fg	Enzyme	fm(E)	Fg	[I]ug (µM)	I Optimized [I] (µM)	Ki (µM)				Dose	Cmax (µM)	kabs (min-1)	Fa.Fg	Qh	Fu(blood)	Rb	Kb	
							Value	[C]prot	Substrate	fu(mic)									
1	1	CYP2C9	0.22		2.622	+ 1.77	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.014	1	1.61	1	0.55	1	
1	1	CYP3A4	0.78		1.226	+ 1.51	46.6	0.2 g/L	Midazolam		0.02 g	+ 2.33	+ 0.006	1	1.61	1	0.55	1	
1	1	CYP2C9	0.22		2.452	+ 3.009	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.64	+ 0.006	1	1.61	1	0.55	1	
1	1	CYP3A4	0.78		5.244	+ 3.529	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.64	+ 0.014	1	1.61	1	0.55	1	
1	1	CYP2C9	0.22		2.452	+ 3.047	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.71	+ 0.006	1	1.61	1	0.55	1	
1	1	CYP3A4	0.78		5.244	+ 3.568	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.71	+ 0.014	1	1.61	1	0.55	1	
1	1	CYP2C9	0.22		1.226	+ 1.13	81.5	0.2 g/L	Diclofenac		0.02 g	+ 1.64	+ 0.006	1	1.61	1	0.55	1	
1	1	CYP3A4	0.78		2.622	+ 1.391	46.6	0.2 g/L	Midazolam		0.02 g	+ 1.64	+ 0.014	1	1.61	1	0.55	1	
1	1	CYP2C9	0.22		2.452	+ 2.046	81.5	0.2 g/L	Diclofenac		0.04 g	+ 2.89	+ 0.006						
1	1	CYP3A4	0.78		2.452	+ 2.046	46.6	0.2 g/L	Midazolam		0.04 g	+ 2.89	+ 0.006						
1	1	CYP2C9	0.22		1.226	+ 1.51	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.006						
1	1	CYP3A4	0.78		2.622	+ 1.77	46.6	0.2 g/L	Midazolam		0.02 g	+ 2.33	+ 0.014						

预测是输入的数据值

点击数字了，可以看到该结构是依据什么数据来源进行计算

Protocol details

**Article:**  
Drug Metab Dispos. 2004; 32, 821-827 (Li, Xue-Qing; Andersson, Tommy B; Ahlstrom, Marie; Weidolf, Lars.)

**TARGET (Widil):** SwissProt: P11712, GeneID: 1559, PDB: 1OG2, 1OG5, 1R90  
Human Cytochrome P450 2C9  
- Non Transfected

**Protocol : Enzymology : Inhibition**

**BIOLOGICAL MATERIAL:**  
Animal: Animal Cell/Unicellular Fraction  
Species: Human  
Tissue: Definition: Liver  
Cell: Definition: (Microsome)  
Amount: Protein:0.2 mg/mL

**EXPERIMENTAL CONDITIONS - Protocol : Enzymology : Inhibition**  
Compound Action: Inhibition of Basal activity

**Substrate Type:** Exogenous  
Substrate: Diclofenac (Km=5.3 µM)  
Coenzyme: NADPH (1 mM)  
Incubation: 15 minute (pH:7.4) in:200µL  
---Buffer: Tris-HCl  
---Buffer composition: Tris-HCl (0.1 M)

**Relevant Measurement Publications:**  
Aliment Pharmacol Ther. 2001; 15, 1929-37  
Eur J Clin Pharmacol. 2001; 57, 485-92  
Br J Clin Pharmacol. 1998; 45, 369-75  
Br J Clin Pharmacol. 1996; 42, 249-52  
Clin Pharmacol Ther. 1995; 58, 159-64

**Biological Activities**

Detailed Headings	KI more...		KI more...		
	4-Hydroxylation	4-Hydroxydiclofenac	4-Hydroxylation	4-Hydroxydiclofenac	
MOLECULE	Conc/Dose	value(µM)	S.D.	value(µM)	S.D.
(+)-Omeprazole	162828	5.3	0.4		



# 导出数据-结果总览

Victim	Perpetrator1		AUC Ratio								
	Name	Therapeutic class	Dose/unit	Min	Max	Mean	SD	Median	5th Perc.	95th Perc.	Count
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.065 g	1.061	1.062	1.061	5.003E-4	1.061	1.061	1.062	2
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.6 g	1.554	1.554	1.554	4.065E-5	1.554	1.554	1.554	2
Test	(+)-Warfarin	~Antithrombotic~	0.007 g	1.075	1.075	1.075	0.0	1.075	1.075	1.075	1
Test	(-)-Omeprazole	~Ant ulcerative~Proton pump inhibitor~	0.02 g	1.022	1.038	1.032	0.004	1.033	1.023	1.037	24
Test	(-)-Omeprazole	~Ant ulcerative~Proton pump inhibitor~	0.04 g	1.03	1.078	1.059	0.013	1.062	1.034	1.075	64
Test	(-)-Warfarin	~Antithrombotic~	0.007 g	1.033	1.142	1.094	0.035	1.096	1.045	1.135	5
Test	AMG 487		0.025 g	2.82	2.82	2.82	0.0	2.82	2.82	2.82	1
Test	AMG 487		0.1 g	7.778	7.778	7.778	0.0	7.778	7.778	7.778	1
Test	AMG 487		0.25 g	18.223	18.223	18.223	0.0	18.223	18.223	18.223	1
Test	Acamprosate		0.3 g	1.012	1.086	1.046	0.02	1.043	1.017	1.079	441
Test	Acamprosate		0.5 g	1.017	1.141	1.075	0.033	1.069	1.026	1.129	441
Test	Acamprosate		0.666 g	1.019	1.184	1.095	0.043	1.088	1.03	1.167	441
Test	Acamprosate		0.8 g	1.025	1.223	1.117	0.052	1.108	1.038	1.203	441
Test	Acamprosate		1.0 g	1.012	1.271	1.132	0.065	1.123	1.03	1.241	882
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	0.65 g	4.048	4.105	4.076	0.018	4.079	4.048	4.103	24
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	1.0 g	4.053	4.134	4.093	0.026	4.098	4.054	4.133	48
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.325 g	1.753	1.825	1.789	0.029	1.789	1.756	1.823	4
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.96 g	3.395	3.607	3.5	0.086	3.499	3.401	3.6	4
Test	Adefovir dipivoxil	~Anti-HIV~Antiviral~	0.01 g	1.022	1.106	1.064	0.042	1.064	1.026	1.102	2
Test	Adefovir	~Antiviral~	0.01 g	1.001	1.001	1.001	0.0	1.001	1.001	1.001	2
Test	Aliskiren	~Antihypertensive~	0.04 g	1.002	1.006	1.004	0.002	1.004	1.002	1.006	24
Test	Aliskiren	~Antihypertensive~	0.08 g	1.003	1.011	1.007	0.004	1.007	1.003	1.011	24
Test	Aliskiren	~Antihypertensive~	0.16 g	1.006	1.023	1.014	0.008	1.014	1.006	1.023	24
Test	Aliskiren	~Antihypertensive~	0.3 g	1.013	1.056	1.032	0.018	1.031	1.013	1.053	408
Test	Aliskiren	~Antihypertensive~	0.64 g	1.026	1.095	1.06	0.033	1.059	1.026	1.095	24
Test	Aliskiren	~Antihypertensive~	0.85 g	1.036	1.132	1.083	0.046	1.081	1.036	1.132	24
Test	Aliskiren	~Antihypertensive~	1.2 g	1.051	1.184	1.116	0.064	1.114	1.051	1.184	24
Test	Aliskiren	~Antihypertensive~	1.8 g	1.073	1.258	1.164	0.089	1.162	1.073	1.258	24
Test	Alosetron	~Antiemetic~	0.001 g	1.003	1.014	1.007	0.002	1.006	1.004	1.01	2704
Test	Alosetron	~Antiemetic~	0.002 g	1.006	1.028	1.014	0.004	1.013	1.008	1.021	2028
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	0.001 g	1	1.001	1	1.289E-4	1	1	1.001	245
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	2.5E-4 g	1	1	1	2.245E-5	1	1	1	35
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	5.0E-4 g	1	1	1	4.758E-5	1	1	1	70
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	6.3E-4 g	1	1.001	1	5.657E-5	1	1	1	35
Test	Alvimopan	~Laxative~	0.006 g	1.003	1.009	1.005	0.002	1.005	1.003	1.009	242
Test	Alvimopan	~Laxative~	0.012 g	1.005	1.019	1.011	0.004	1.01	1.006	1.017	121
Test	Alvimopan	~Laxative~	0.018 g	1.008	1.028	1.016	0.005	1.015	1.01	1.026	121
Test	Alvimopan	~Laxative~	0.024 g	1.011	1.038	1.022	0.007	1.02	1.013	1.034	121
Test	Amitriptyline	~Analgesic: non narcotic~Antidepressant~	0.025 g	1.015	1.23	1.116	0.042	1.117	1.047	1.193	1728
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.005 g	1.438	1.955	1.657	0.174	1.645	1.438	1.954	245
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.01 g	2.224	2.51	2.337	0.093	2.321	2.226	2.508	245
Test	Amoxicillin	~Antibiotic~	1.0 g	1.048	1.154	1.097	0.039	1.096	1.048	1.154	27
Test	Amprenavir	~Antiviral~	0.45 g	4.545	4.545	4.545	1.505E-5	4.545	4.545	4.545	16
Test	Amprenavir	~Antiviral~	0.6 g	4.545	4.545	4.545	1.19E-5	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	0.9 g	4.545	4.545	4.545	7.026E-6	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	1.2 g	4.545	4.545	4.545	6.297E-6	4.545	4.545	4.545	12
Test	Aprepitant	~Antiemetic~	0.08 g	0.159	0.386	0.27	0.105	0.267	0.161	0.383	4
Test	Aprepitant	~Antiemetic~	0.25 g	0.207	0.491	0.349	0.142	0.349	0.221	0.477	2
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.001 g	1	1	1	7.301E-6	1	1	1	81
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.002 g	1	1.001	1.001	2.586E-5	1.001	1	1.001	162
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.003 g	1	1.001	1.001	2.76E-4	1.001	1.001	1.001	405

## Bar chart information

The bar chart displayed in the DDI table is a color coded graphical overview of the risk assessment.

Color codes represent AUCi/AUC ratio ranges corresponding to the FDA classification [1] of CYP inhibitor and inducer potency. The size of each colored segment in the bar represents the percentage of the total number of calculated AUC ratios (for a given victim/perpetrator couple) that falls into one of the following categories:

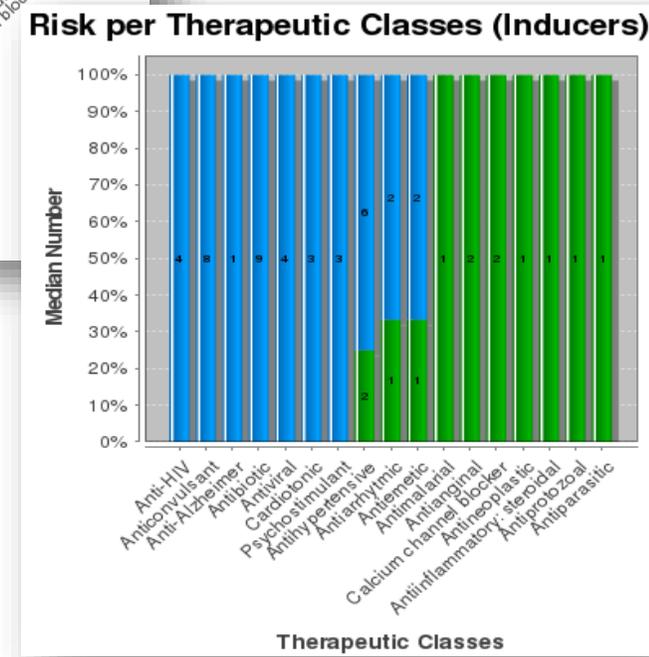
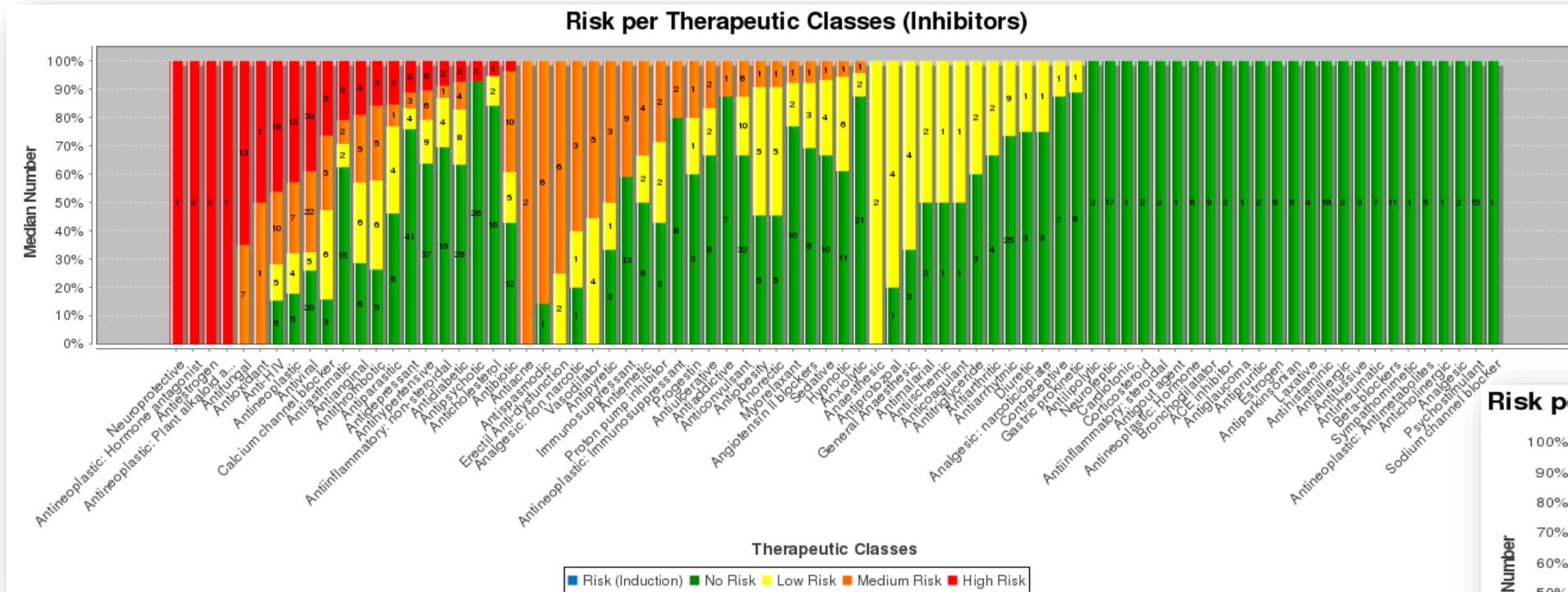
Category	AUC ratio range		Colour
Risk(Induction)		AUC ratio <	0.8
No risk	0.8	≤ AUC ratio <	1.25
Low risk	1.25	≤ AUC ratio <	2
Medium risk	2	≤ AUC ratio <	5
High risk	5	≤ AUC ratio	

[1] <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...>

# 导出数据-预测结果输入的数据

DDI Risk Calculator (DDIRC) Version : 2017.1			
DDIRC database Version: October 2015			
Date: 2018.05.01			
<b>Victim drug Test</b>			
<b>Metabolism</b>			
<b>Enzymes</b>	Name	CYP2C9	CYP3A4
	kdeg(min-1)	1.1E-4	3.2E-4
<b>fm(E) calculation</b>	fm(E)	0.22	0.78
	Method used	recombinant (ISEF)	recombinant (ISEF)
	RAF		
<b>Scaling factor</b>	ISEF	0.86	0.32
	Liver Abund. (pmol/m	69.6	173
<b>Kinetic</b>	Clint (µl/min/pmol)	0.025	0.094
	Km (µM)	4	32
	Vmx (pmol/min/pmol	0.1	3
	[C] prot. (g/l)	0.5	0.5
<b>Hepatic fraction</b>	fh	1	
	Method used	Predicted	
<b>Clearance</b>	Method used	Predicted	
	Cl (L/h)	17.07	
	Cl non hepatic (L/h)	0.0	
	ClH (L/h)	17.07	
	fup	0.4	
	Qh (L/min)	1.61	
<b>Non specific binding</b>	fu(mic)	0.399	
	[C]prot (g/L)	0.5	
<b>fu(mic) calculation</b>	Method	Hallifax	
	LogP	4.28	
	pKa	7.66	
<b>Gut Metabolism</b>	Fg	1	
	Method used	User defined	
	Qg (L/h)	18	
	fug	1	
<b>F'g/Fg estimation</b>	Method	Model predicted	
<b>Perpetrator drug</b>			
	<b>Perpetrator 1</b>		
	Dosing regimen	Repeated	
<b>Estimated Liver Concentration</b>	[i]in estimati	(Optimized [!])	
<b>Blood or Plasma Binding</b>	fu plasma	No	
<b>Non Specific Binding</b>	fu(mic)	No	
	fu(hep)	No	
<b>inhibitory constant</b>			
<b>Enzyme</b>	<b>Perpetrator</b>		
	Value	Perpetrator Nam	[C]prot (g/L kinact (min-1 Emax nH Induction Type Victim[C] (µM Victim Km (µM)

# 导出结果-测试药物对每种药物分类的风险总览



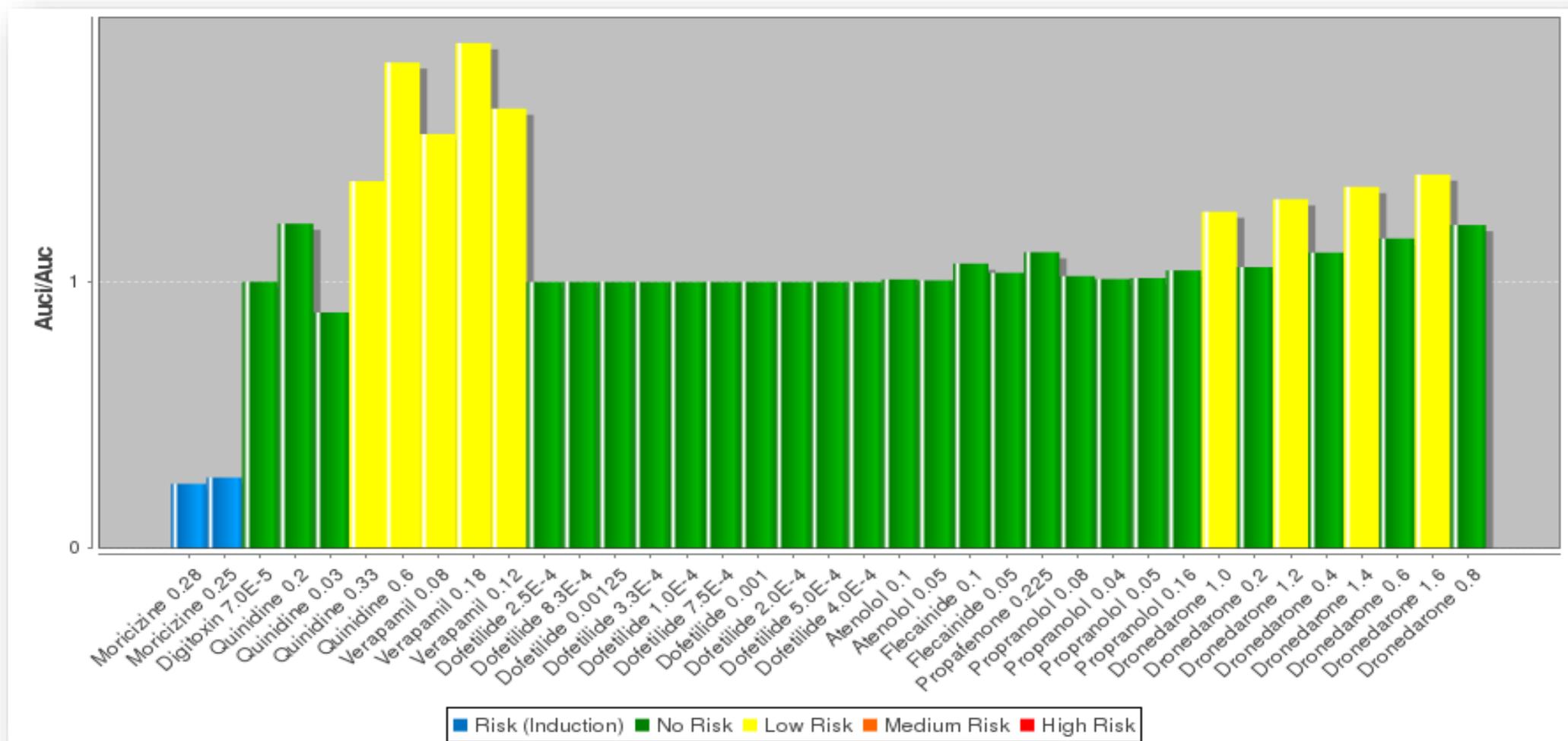
# drugs in tested in each class is indicated







# 问题 – 与抗心律不齐药的潜在风险



# Question: 测试化合物与对乙酰氨基酚作用风险?

- 检索治疗类镇痛药，非麻醉药
  - 注: DDIRC中的药物分类与PharmaPendium中是不一样的
- 查找对比中等风险的结果 (Average AUC ratio of ~4)

PharmaPendium® Browse ▾ Search ▾ My tools new

DDI Prediction 3 records from DDI Risk Calculator: Victim: test

Refine search results: Apply Clear All

**Therapeutic Classes**

- Analgesic: non narcotic (3)
- Antidepressant (1)
- Antiinflammatory: non-steroidal (1)
- Antipyretic (2)
- Antithrombotic (1)

**Molecules** ▾

**Drug Type** ▾

**Results**

ID	Perpetrator ▾	Dose ▾	MBI ▾	AUC Ratio ▾	C
1	<b>Acetaminophen</b> 99468 Analgesic: non narcotic Antipyretic Drug Type: Approved	Multiple		<div style="width: 100%; height: 15px; background-color: orange;"></div>	72
2	<b>Acetylsalicylic acid</b> 34524 Antithrombotic Analgesic: non narcotic Antiinflammatory: non-steroidal Antipyretic Drug Type: Approved	Multiple		<div style="width: 100%; height: 15px; background-color: yellow; border-right: 1px solid orange;"></div>	8
3	<b>Amitriptyline</b> 4815 Analgesic: non narcotic Antidepressant Drug Type: Approved	0.025 g		<div style="width: 100%; height: 15px; background-color: green;"></div>	17

# DDIRC Demo: Test compound as a perpetrator

# Predict DDIs with the proprietary drug as a perpetrator

## DDI risk calculator

### Predict DDI: Proprietary Victim Drug

Start

Predict all interactions of your proprietary victim drug vs all perpetrators in DDI Knowledgebase

### Predict DDI: Proprietary Perpetrator Drug

Start

Predict all interactions of your proprietary perpetrator drug vs all victim drugs in DDI Knowledgebase

# Predict DDIs with the proprietary drug as a perpetrator

PharmaPendium

Browse Search My tools IP-authorized

## Proprietary Perpetrator Drug

Perpetrator 1 Perpetrator 2 Victim

Perpetrator definition

\*Compound name:  \*Mol. Weight:  g/mol \*Dose:  mg **1**

Dosing regimen

Absorption: first order model

Single  Repeated

\*Fa.Fg:  **1** **Calculate kabs** **2**

\*kabs (min-1):  **0.1**

Estimated liver concentration

[J]in (hepatic estimation)

Optimized [J] \*Qh:  **1.61** L/min

Cavg  ng/mL

[J]in,avg  max:

Cmax

[J]in,max

Non equilibrium

Kp:

or

Kb:

or

C/M:

Plasma binding and blood/plasma ratio

\*fup:  **1**  \*Rb:  **0.55** **4**

Perpetrator Inhibitory constant

Microsomal binding

fu(mic):  Prot. conc.:  g/L **Calculate fu(mic)** **5**

Hepatocyte binding

fu(hep):  10e6 Cell/ml **Calculate fu(hep)** **6**

Competitive Inhibition

Enzyme(s)	Parameter ( $\mu\text{M}$ )	Value	[C]prot (g/l)	Substrate name	Victim C ( $\mu\text{M}$ )	Victim Km ( $\mu\text{M}$ )
Select	Select	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Mechanism Based (MBI)

Enzyme(s)	kdeg (min-1)	Parameter ( $\mu\text{M}$ )	Value	[C]prot (g/l)	kinact Value (min-1)	Substrate name
Select	<input type="text"/>	Select	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Induction

Enzyme(s)	Parameter ( $\mu\text{M}$ )	Value	E <sub>max</sub>	nh	Induction type	Substrate name
Select	Select	<input type="text"/>				

Predict interactions

Feedback

1. Enter compound name, molecular weight (473.5) and dose (40 mg QD repeated dose)
2. Default absorption values are worst-case scenario ( $F_a=1$ )
3. Choose the model: maximal systemic concentration in blood entering into the liver and add  $C_{max}$  (331.5 ng/ml)
4. Change  $F_{up}$  value = 0.4
5. Calculate  $F_u(\text{mic})$ :  $P_{ka} = 7.66$ ,  $[C]_{\text{prot}}=0.2$ ,  $\text{Log}P = 4.28$
6. No values are necessary for hepatocyte binding
7. Cyp3A4 values =  $\text{IC}_{50}$ , Value = 3.6,  $[C]_{\text{prot}} = 0.2$ , Substrate name = midazolam

# Predict DDIs with the proprietary drug as a perpetrator

Perpetrator definition  
 \*Compound name: test \*Mol. Weight: 4736 g/mol \*Dose: 40 mg

Dosing regimen  
 Single  Repeated  
 Absorption: first order model  
 \*Fa.Fg: 1 Calculate kabs  
 \*kabs (min-1): 0.1

Estimated liver concentration  
 [I]in (hepatic) estimation  
 Optimized [I] \*Qh: 1.61 L/min  
 Cavg \* Cmax: 331.5 ng/mL  
 [I]in.avg  
 Cmax  
 [I]in.max  
 Non equilibrium  
 Kp:  
 or  
 Kb:  
 or  
 C/M:

Plasma binding and blood/plasma ratio  
 \*fup: 0.4  \*Rb: 0.55

Perpetrator Inhibitory constant  
 Microsomal binding  
 fu(mic): 0.624 \* Prot. conc.: 0.2 g/L Calculate fu(mic)  
 Hepatocyte binding  
 fu(hep): 10e6 Cell/ml Calculate fu(hep)

Competitive Inhibition

Enzyme(s)	Parameter (µM)	Value	[C]prot (g/l)	Substrate name	Victim C (µM)	Victim Km (µM)
CYP3A4	Ki	3.6	0.2	Midazolam		
Select	Select			select molecule		

Mechanism Based (MBI)

Enzyme(s)	kdeg (min-1)	Parameter (µM)	Value	[C]prot (g/l)
Select		Select		

Induction

Enzyme(s)	Parameter (µM)	Value	Emax	nh
Select	Select			

Repeated Doses 40mg QD  
 Cmax = 331.5 ng/ml at steady state  
 Kabs=0.1 min-1  
 Fa=1  
 fup=0.4  
 fu(mic)=0.624 at [C]prot=0.2mg/ml

fu(mic) Calculation

Pka: 7.66  
 Prot. conc.: 0.2 g/L  
 LogP: 4.28

Hallifax/Houston  
 Austin

Calculate

Molecule Search

Select molecules containing: midazolam

Name	Synonyms
1'-4-Dihydroxymidazolam	
1'-Hydroxymidazolam	Ro 21-6347; alpha-hydroxy-midazolam; 1-Hydroxymidazolam
1'-Hydroxymidazolam glucuronide	
1'-Hydroxymidazolam N-glucuronide	
4-Hydroxymidazolam	
Midazolam	Dormicum; Midosed; Rohipnol
Midazolam N-glucuronide	

# Enter intestinal metabolism values for the Victim

## Proprietary Perpetrator Drug

Perpetrator 1 Perpetrator 2 Victim

Please select the database retrieval rules for the victim drugs:

First Pass Metabolism (gut wall)

Use Fg

Intestine inhibition : Estimation of Fg'/Fg ratio

Maximal Inhibition (F'g/Fg)=1/Fg

Model Predicted

Qg L/h

Predict interactions

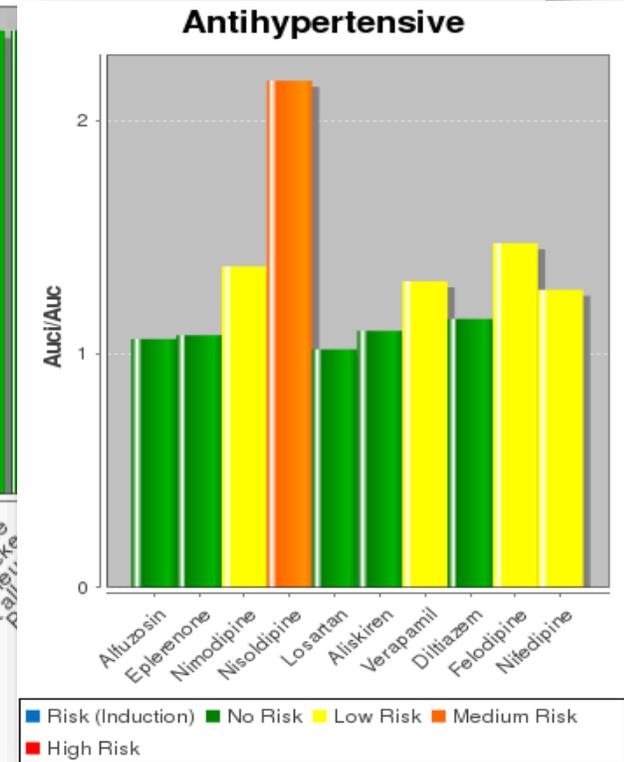
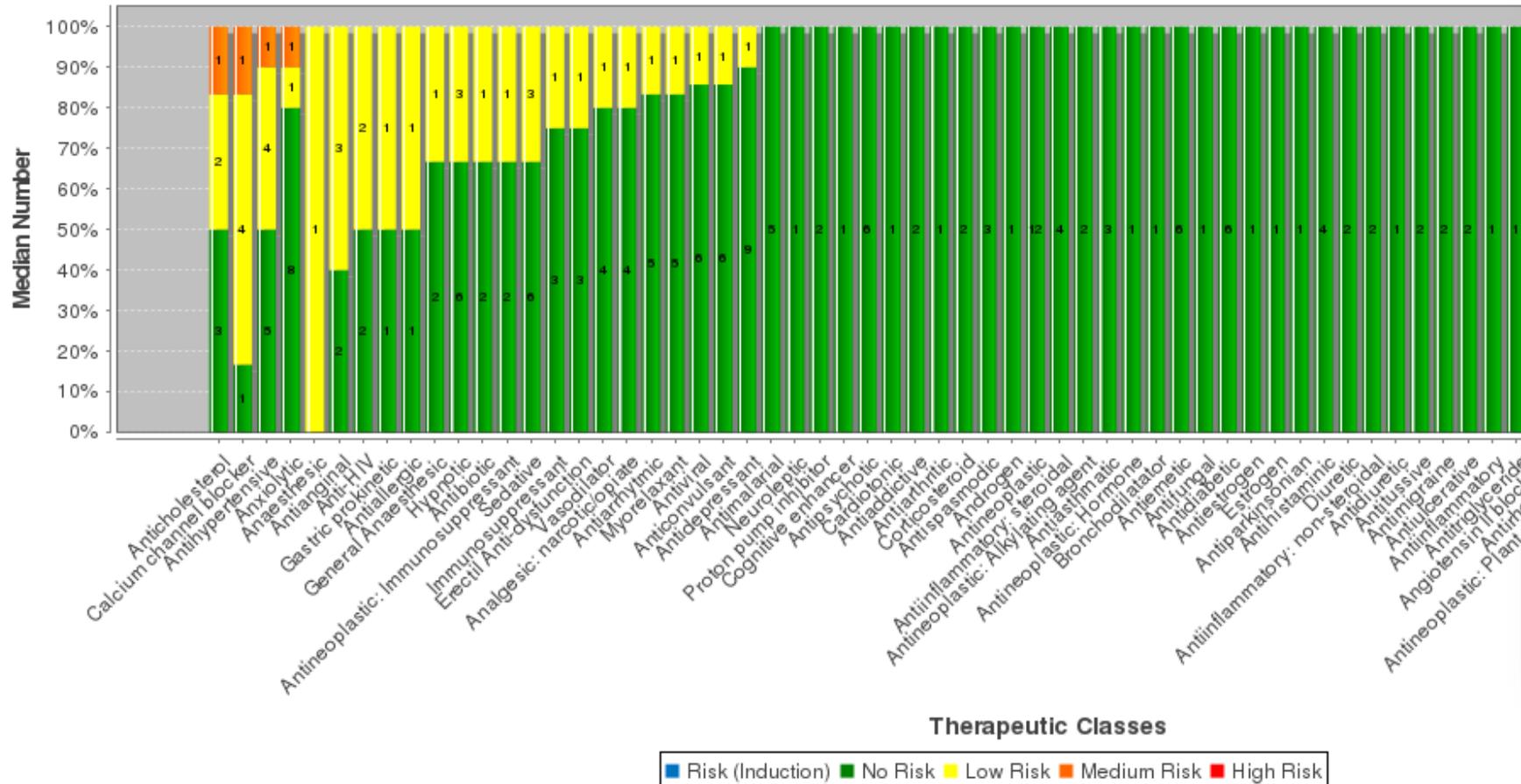
When CYP3A4 or CYP3A5 is selected, there is the option to define if & how intestinal metabolism should be taken into account.

The Fg values will be retrieved from the DDIRC library. If no values are found then a default value of 1 will be used.

If "Use Fg" is unselected, then a default value of 1 is used for calculation which assumes no metabolism in the gut for the victim.

# There may be a risk with anticholesterol and antihypertensive drugs

Risk per Therapeutic Classes (Inhibitors)



# 小结

- 1. PharmaPendium运用信息分类和文本挖掘技术，对FDA/EMA的官方档案进行再处理，能够帮助用户快速获取原文关键信息，尽可能避免关键信息缺失导致的不良后果。
- 2. PharmaPendium对FDA/EMA的原文中的数据信息进行深度的提取，归类，整理，便于用户进行大数据分析，辅助实验方案制定，更好的达到实验预期，管控成本。
- 3. PharmaPendium依据FDA指南进行文本信息的整理，归拢证据，更好的与监管机构沟通，使药物审批的沟通更有效率。

Thank you

