



如何利用Pharmapendium数据库支持药物研发

张弦 吴鹏 Elsevier 生命科学 解决方案经理

CONTENTS 目录

1 Pharmapendium涵盖内容及特点

2 Pharmapendium的数据优势

3 利用Pharmapendium 进行临床前及临床信息检索

1. 毒理与药物安全信息检索

2. 药效信息的检索

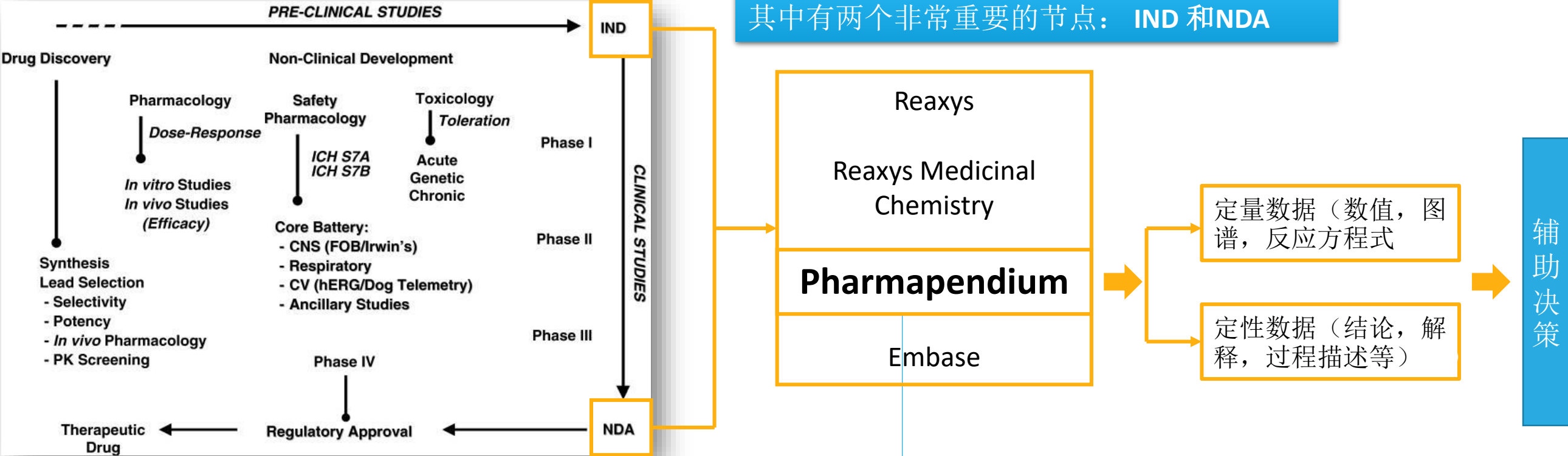
3. 药代动力学信息的检索

4 利用Pharmapendium 进行药物相互作用风险预测 (DDI Risk)



药物研发中面临的挑战

在药物研发中，为了确保药物能够顺利上市，其中有两个非常重要的节点：**IND** 和**NDA**



查找
FDA/AC
reports

借鉴里面的
意见和问题

查找药物QT
信息，数据

参考辅助药
物研发

上市药物临
床终点，替
代终点信息

辅助临床方
案设计

总结 ‘indications’
为基础的 ‘安慰剂
(placebo) 组效
应’

辅助临床方案设计

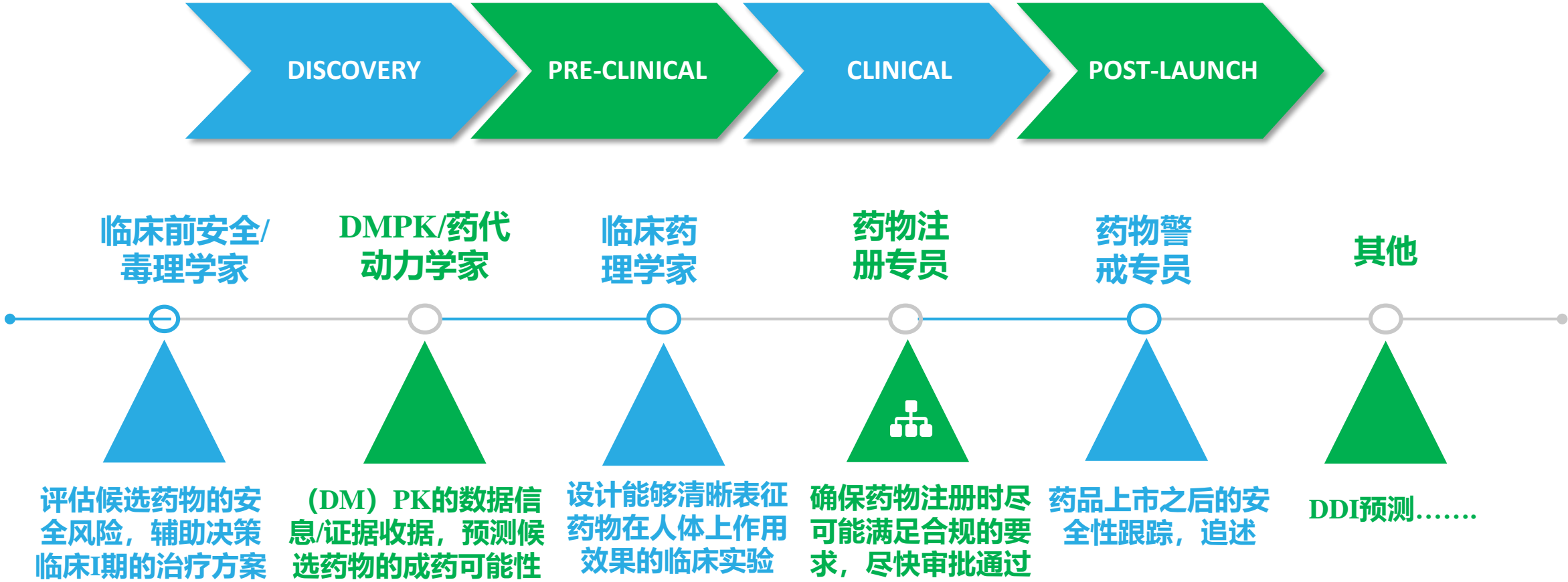
检索上市药物
动物模型设计
方案与数据

参考选择合适的
动物模型？

检索与分析
不同的种族的
‘血浆蛋白结合率
差异’

快速找到 ‘血
浆蛋白结合率低’
且对首过
代谢酶有抑制
性的药物相关
信息，及其研
究方法

临床前，临床信息检索的动机/挑战



01

ParmaPendium-涵盖内容与特点

PharmaPendium数据涵盖的范围

FDA数据

所有经过FDA审批通过的上市药物，在FDA的文件包中从临床前-上市实验数据，包含DMPK，毒理，药效，剂量，副作用等（包含以前的纸版数据FDA无法查询）

EMA数据

所有经过EMA审批通过的上市药物，在EMA的文件包中从临床前-上市实验数据，包含DMPK，毒理，药效，剂量，副作用等

FDA AERS

提交给FDA的药物上市以后不良反应事件报告

FDA评审委员会

FDA评审委员会，会议记要

其他来源：
临床医学著名书籍
Meyler/Mosbyb，
部分临床相关杂志
等

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

2.29M+

pages of FDA
approval
documents

200K+

pages of EMA
approval
documents

9.45M+

FDA AERS
reports

673K+

Pages from FDA
Advisory
Committee
Meetings

Extracted Data

4450

Drugs
indexed &
fully
searchable

1.6M+

PK data lines

305K+

Metabolizing
enzyme and
transporter data
lines

1.66M+

safety data lines

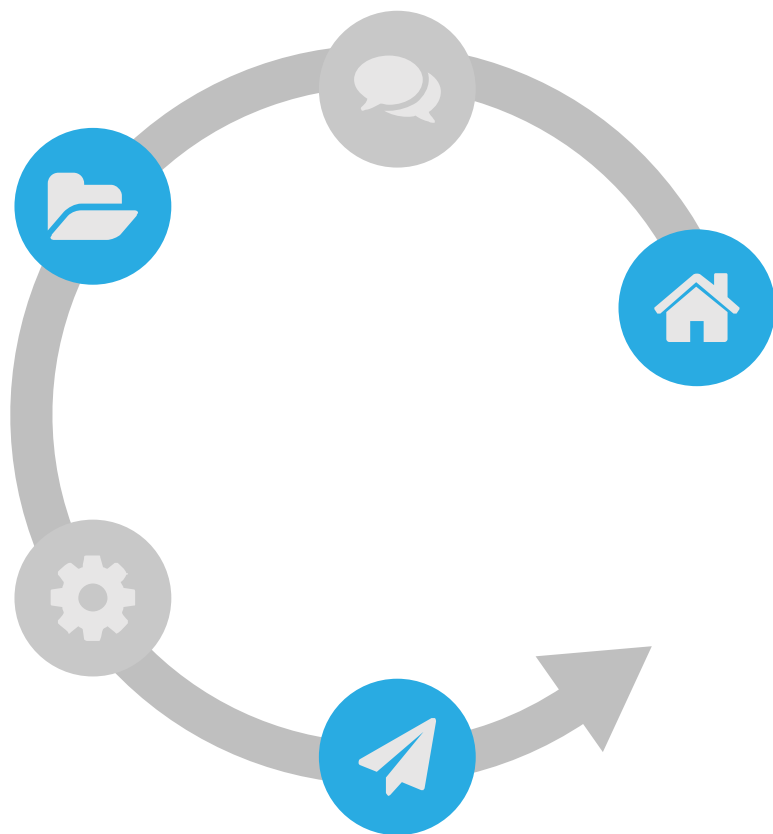
2.45M+

efficacy data
lines

115K+

activity data
lines

PharmaPendium-能获取的直接信息



FDA/EMA.....

- 申请上市成功药物的资料包（临床前-上市），Meyler副作用资料/Mosby药物咨询资料
- 新药上市申报文件/文献/Meyler/Mosbyb资料中的安全性数据
- 通过文字/结构检索FAERS（10M+）中的相关药物不良反应事件 报告
- 1938-1991年FDA纸质报告可电子检索（无法从FDA官网获得）



PK（药代）模型

- FDA/EMA药物申报文件资料中的药代动力学信息的提取，并能快速建立各种数据的比较（相似结构，相同/不同适应症等）



MET（转运酶）模型

- FDA/EMA药物申报文件资料/文献中的转运酶信息的提取，并能快速建立各种数据的比较（相似结构，相同/不同适应症等）
- 提供计算器，结合PK数据进行DDI效果预测



药效模型

- FDA/EMA药物申报文件资料中的药效模型信息的提取，文献中报道的药效模型信息的获取

PharmaPendium与 Drugs@FDA比较

	PharmaPendium	Drugs@FDA
Starting year	1938–	1998–
PDF data style	Picture & Text	Picture only (Only latest documents with text)
Search	Full text Searchable ; Drug class/ Target class searchable ;	Select from Drug name
Download	OK	OK
Index	Toxicity and Adv. Effects are indexed by experts	Not indexed

02

PharmaPendium-数据优势

如何在FDA的官网上获得相关药物的Approval Package

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Home Food Drugs Medical Devices

Opioid and Nicotine Use Recovery: Influences
Scientific Conference
Sept 27-28, 2018

SAVE the Date!
Join researchers, clinicians and policy experts to discuss the influences on substance use, misuse, and recovery.

Recalls & Alerts

- Recalls
- MedWatch: Safety Alerts

Approvals

- Enforcement
- Industry

FILTER SEARCH RESULTS

FILTER BY TOPICS

- Drugs
- Medical Devices
- Advisory Committees
- Public Information & Education

FILTER BY FORMAT

- PDF
- Web pages

SORT BY

Relevance
Date

Clear Filters

gefitinib iressa

Search Results

PDF Iressa (gefitinib) tablets Label

2009-03-31 | www.accessdata.fda.gov/drugsatfda_docs/label/2003/021399lbl.pdf

... DESCRIPTION **IRESSA (gefitinib tablets)** contain 250 mg of **gefitinib** and are available as brown film-coated tablets for daily oral administration. ... **IRESSA (gefitinib) Tablets** CLINICAL PHARMACOLOGY ...

[Text Version](#)

IRESSA (gefitinib) Tablets

www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206995orig1s000toc.cfm

... **IRESSA (gefitinib) Tablets**. Share; Tweet; LinkedIn; Pin it; More sharing options: LinkedIn; Pin it. Email; Print. Company: AstraZeneca UK Limited Application No.: 206995 Approval Date: 07/13/2015. ...

Cached

Drug Approval Package: Iressa (gefitinib) NDA #021399

www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021399_iressa.cfm

... Print; Share; E-mail. FDA Home; Drugs; Drug Approvals and Databases; Drugs@FDA. -. Drug Review Package **Iressa (gefitinib) Tablets** Company: AstraZeneca Application No.: 021399 Approval Date: 5/5/2003. ...

Cached

Drug Approval Package

Drug Approval Package

[FDA Home](#) [Drugs](#) [Drug Approvals and Databases](#) [Drugs@FDA](#)

Drug Review Package
Iressa (gefitinib) Tablets
Company: AstraZeneca
Application No.: 021399
Approval Date: 5/5/2003

- [Approval Letter\(s\) \(PDF\)](#)
- [Printed Labeling \(PDF\)](#)
- [Medical Review\(s\) \(PDF\)](#)
[Part 1 \(PDF\)](#)
[Part 2 \(PDF\)](#)
- [Chemistry Review\(s\) \(PDF\)](#)
- [Pharmacology Review\(s\) \(PDF\)](#)
[Part 1 \(PDF\)](#)
[Part 2 \(PDF\)](#)
- [Statistical Review\(s\) \(PDF\)](#)
- [Microbiology Review\(s\) \(PDF\)](#)
- [Clinical Pharmacology Biopharmaceutics Review\(s\) \(PDF\)](#)
- [Administrative Document\(s\) \(PDF\)](#)
[Part 1 \(PDF\)](#)
[Part 2 \(PDF\)](#)
[Part 3 \(PDF\)](#)

Date created: July 15, 2003

[Back to Top](#) [Drugs@FDA](#)

CLINICAL REVIEW

Study type	Study pts.	Sample Size (N)	Design	1 ^o endpoint	2 ^o 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 \leq 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 \leq 20	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06

BSC=best supportive care; DFS=disease free survival; LCS= Lung cancer subscale;
PFS=progression free survival;
PS=performance status; OS=overall survival

Pharmapendium直接定位出关于Gefitinib中clinical review的PDF文件以及相应的位置

PharmaPendium®

FDA Approval Package

clinical review

2015-06-04 PDF(1305k)

Other Important Information from FDA > Cross Discipline Team Leader Review 206995/S-000 Part 01

... Pharmaceuticals LP September 17, 2014 July 17,2015 Iressa (Gefitinib)

Clinical Review Primary/ Secondary Reviewer ...

2003-01-31 PDF(2024k)

Medical/Clinical Review > Medical/Clinical Review 021399/S-000 Part 01

... Review(s) CLINICAL REVIEW Clinical Review NDA 21-399 Drug Name Medical Reviewer Martin H. Cohen, M.D ...

2015-06-04 PDF(914k)

Other Important Information from FDA > Cross Discipline Team

Browse Search My tools new

FDA Approval Package - Gefitinib > Medical/Clinical Review

Medical/Clinical Review 021399/S-000 Part 01

clinical review 26/198 Go

CLINICAL REVIEW

Study type	Study pts.	Sample Size (N)	Design	1 ^o endpoint	2 ^o 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

12 of 66

Pharmapendium检索界面直观清晰—支持结构，靶点，适应症检索

PharmaPendium®

Browse ▾

Search ▾

My tools new

Peng Wu

Quick Search

All These Sources

Drugs

Adverse Effects/Toxicity

Targets

Indications

e.g. Coronar* artery disorders

Search >

☐ Include synonyms

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

Pharmacokinetic Data

Metabolizing Enz. & Trans. Data

Drug Safety Data

FAERS Data new

Chemistry Search

Efficacy Data

Activity Data

DDI risk calculator

不良反应报告

DDI预测

结构式检索

ELSEVIER

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RELX Group™

PharmaPendium-数据的优势

➤ 上市药物-结构直接检索----从临床前至上市后所有相关信息 (FDA, EMA) 打包直接获得

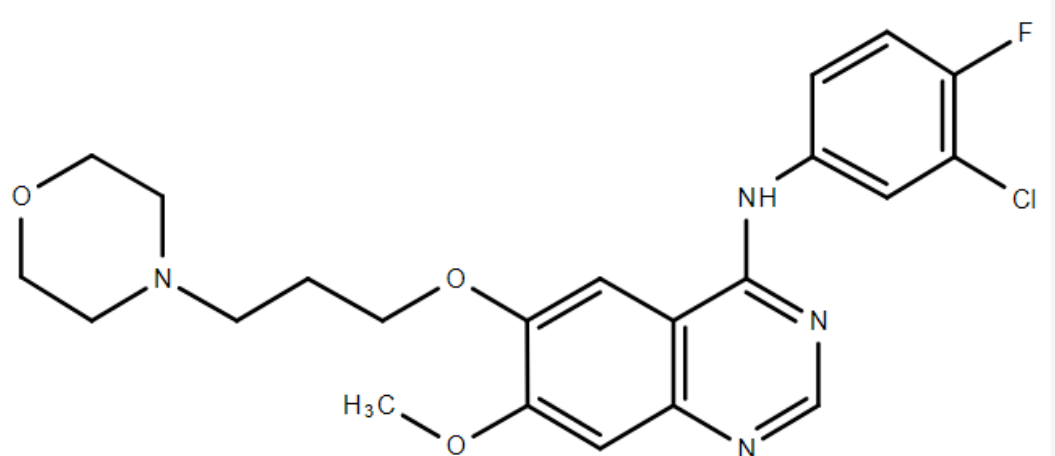
PharmaPendium® Browse ▾ Search ▾ My tools new

Chemistry search

Search criteria

Chemistry Structure

substructure search ▾



The image displays the chemical structure of Gefitinib, a tyrosine kinase inhibitor. It features a central quinazoline ring system. At position 2, there is a morpholine ring connected via a propyl chain. At position 4, there is a methoxy group (-OCH3). At position 6, there is an amino group (-NH-) connected to a 2-chloro-3-fluorophenyl ring.

Browse drugs - Antineoplastics > Antineoplastics, signal transduction inhibitors

Gefitinib

Brands: Gefitinat; Iressa

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

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

Classes: [Antineoplastics, signal transduction inhibitors](#)

Primary targets: [Tyrosine Kinases ^{\(2\)}](#)
[Vascular Endothelial Growth Factor Receptor 2 \(VEGFR2\) ^{\(1\)}](#)

(1) Drug/Target association is from FDA approval packages
(2) Drug/Target association is from Mosby's Drug Consult™

Indications: [Carcinoma lung](#)

PharmaPendium-数据的优势

➤ 药物-临床前-临床-上市后，各阶段毒理-副作用信息

Adverse Effects / Toxicity*:


[Viewing by area affected](#) [View by name](#)

Preclinical
Data
view all 139

Clinical
Data
view all 751

Post-Marketing
Reports (AERS)
view all 7412

+ Blood and lymphatic system disorders	4	20	603
+ Cardiac disorders	2	25	483
+ Congenital, familial and genetic disorders	no data	no data	8
+ Ear and labyrinth disorders	no data	no data	39
+ Endocrine disorders	2	no data	31
+ Eye disorders	3	35	227
+ Gastrointestinal disorders	14	139	1972
+ General disorders and administration site conditions	5	57	2284
+ Hepatobiliary disorders	8	16	755
+ Immune system disorders	no data	2	45
+ Infections and infestations	no data	69	1427
+ Injury, poisoning and procedural complications	no data	no data	140
+ Investigations	51	61	

Feedback 

PharmaPendium-数据的优势

➤ 快速横向比较 ‘同靶点’ 各种上市药物的临床前-临床数据-----有助临床实验设计，IND,NDA报告信息采集

Preclinical Data Clinical Data All Data preclinical and clinical data

ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value
1	Acalabrutinib	Human	healthy	100 mg	Oral	CL/F	159.0 L/h
2	Acalabrutinib (Radiolabelled)	Human					
3	Acalabrutinib	Human					
4	Acalabrutinib	Human					
5	Acalabrutinib	Human					
6	Acalabrutinib	Human					

Preclinical Data Clinical Data All Data preclinical and clinical data

ID	Drug	Parameter	Parameter Value	SD	t	Concomitant	Source	Year
4	Acalabrutinib	-tau)	1111.0 ng*h/mL				FDA approval package document: Label (Page:9) View Full Study PDF 691k	2017
5	Acalabrutinib	median)	0.75 h				FDA approval package document: Label (Page:9) View Full Study PDF 691k	2017
6	Acalabrutinib		34.0 L				FDA approval package document: Label (Page:10) View Full Study PDF 691k	2017
7	Acalabrutinib	plasma ratio	0.7 dimensionless				FDA approval package document: Label (Page:10) View Full Study PDF 691k	2017
8	Acalabrutinib (Radiolabelled)	excretion(radioactivity)	12.0 %				FDA approval package document: Label (Page:10) View Full Study PDF 691k	2017
9	Acalabrutinib	CP-5862 metabolite)(median)	6.9 h				FDA approval package document: Label (Page:10) View Full Study PDF 691k	2017

➤ 分类信息的直接查看-----节约阅读原始文件时间

Drug Monograph

Brand Names

Ingredients

Indications

Description

Clinical Pharmacology

Clinical Studies

Indications

Contraindications

Warnings

Precautions

Interactions

Adverse Reactions

Overdosage

Dosage and Administration

How Supplied

Drug Monograph

Gefitinib

source: Mosby's Drug Consult™ - copyright 2006

ADVERSE REACTIONS).

Clinical Studies

Top ↑

Non-Small Cell Lung Cancer (NSCLC)

A multicenter clinical trial in the US evaluated the tumor response rate of ◀ **gefitinib** ▶ 250 and 500 mg/day in patients with advanced non-small cell lung cancer whose disease had progressed after at least two prior chemotherapy regimens including a platinum drug and docetaxel. ◀ **Gefitinib** ▶ was taken once daily at approximately the same time each day.

Two hundred and sixteen patients (216) received ◀ **gefitinib** ▶, 102 (47%) and 114 (53%) receiving 250 mg and 500 mg daily doses, respectively. Study patient demographics and disease characteristics are summarized in TABLE 1. Forty-one percent (41%) of the patients had received two prior treatment regimens, 33% three prior treatment regimens, and 25% four or more prior treatment regimens. Effectiveness of ◀ **gefitinib** ▶ as third line therapy was determined in the 142 evaluable patients with documented disease progression on platinum and docetaxel therapies or who had had unacceptable toxicity on these agents.

TABLE 1 Demographic and Disease Characteristics

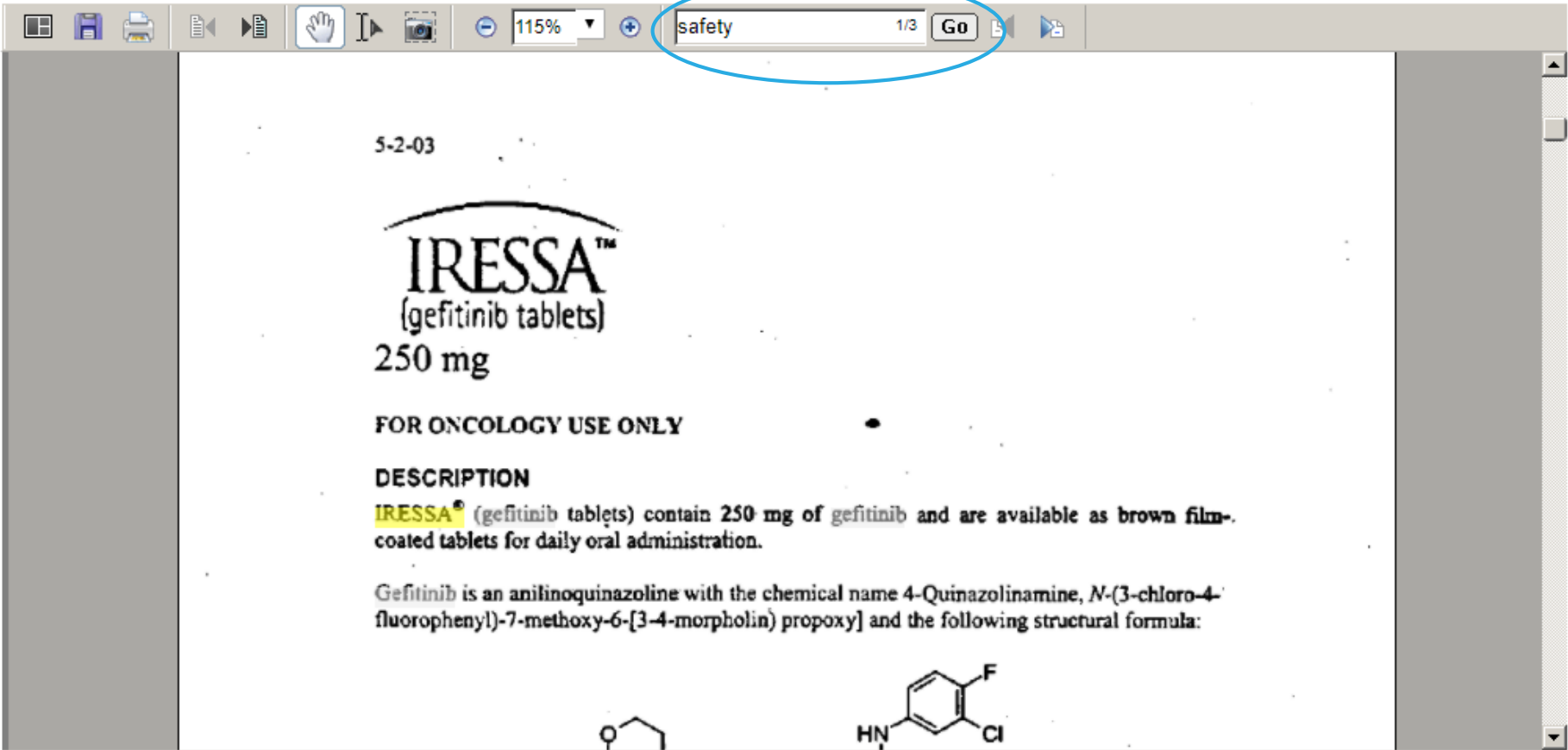
	250 mg/day	500 mg/day
Characteristic	n=66	n=76
Age Group		
18-64 years	43 (65%)	43 (57%)
64-74 years	19 (29%)	30 (39%)
75 years and above	4 (6%)	3 (4%)
Sex		

Feedback 

PharmaPendium-数据的优势

➤ 链接到原始文档-----可直接进行关键词匹配检索

FDA Approval Package - Gefitinib > Printed Labeling
Printed Labeling 021399/S-000



5-2-03

IRESSATM
(gefitinib tablets)
250 mg

FOR ONCOLOGY USE ONLY

DESCRIPTION
IRESSA[®] (gefitinib tablets) contain 250 mg of gefitinib and are available as brown film-coated tablets for daily oral administration.

Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholin) propoxy] and the following structural formula:

COc1cc2c(cnc2c1Nc3ccc(F)c(Cl)c3)C4=CC=CC=C4OCC4

2 of 16

Feedback

对比FDA官网信息检索

➤ FDA官方检索结果VS PharmaPendium检索结果 (aripiprazole)

<ul style="list-style-type: none">• ABILIFY (ARIPIPRAZOLE) NDA #021729 TABLET, ORALLY DISINTEGRATING;ORAL Discontinued OTSUKA• ABILIFY (ARIPIPRAZOLE) NDA #021866 INJECTABLE;INTRAMUSCULAR Discontinued OTSUKA
ABILIFY MAINTENA KIT
ABILIFY MYCITE KIT
ARIPIPRAZOLE
<ul style="list-style-type: none">• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078583 TABLET;ORAL Prescription APOTEX INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078607 TABLET;ORAL Prescription TEVA PHARMS USA• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078608 TABLET;ORAL Prescription TEVA PHARMS USA• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078612 MULTIPLE FORM/ROUTES None (Tentative Approval) BARR LABS INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078613 TABLET; ORAL None (Tentative Approval) BARR LABS INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078614 TABLET; ORAL None (Tentative Approval) SUN PHARMA GLOBAL• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #078708 TABLET;ORAL Prescription TEVA PHARMS USA• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #090165 TABLET, ORALLY DISINTEGRATING; ORAL None (Tentative Approval) ZYDUS PHARMS USA INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #091279 TABLET;ORAL Prescription SANTOS BIOTECH• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #201519 TABLET;ORAL Prescription TORRENT PHARMS LTD• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #202101 TABLET;ORAL Prescription ALEMBIC PHARMS LTD• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #202102 TABLET, ORALLY DISINTEGRATING;ORAL Prescription ALEMBIC PHARMS LTD• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #202547 TABLET, ORALLY DISINTEGRATING;ORAL Prescription ORCHID HLTHCARE• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #202683 TABLET;ORAL Prescription ORCHID HLTHCARE• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #203906 SOLUTION;ORAL Prescription AMNEAL PHARMS• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #203908 TABLET;ORAL Prescription AUROBINDO PHARMA LTD• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #204094 SOLUTION;ORAL Prescription APOTEX INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #204111 TABLET;ORAL Prescription MACLEODS PHARMS LTD• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #204171 SOLUTION;ORAL Prescription LANNETT CO INC• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #204838 TABLET;ORAL Prescription AMNEAL PHARMS• ARIPIPRAZOLE (ARIPIPRAZOLE) ANDA #205064 TABLET;ORAL Prescription HETERO LABS LTD V

➤ 结果文件无分类，需自行阅读辨别

➤ 分门别类整理清晰，可以按需快速找到相应数据

PharmaPendium®	Browse ▾ Search ▾
FDA Approval Package	FDA Approval Package
<div>Search this FDA Package</div> <div><ul style="list-style-type: none">+ Administrative documents+ Approval Letter+ Approval Package+ Chemistry Review+ Clinical Pharmacology and...+ Healthcare Professional S...+ Label+ Letter+ Medical/Clinical Review+ Medication Guide+ Microbiology Review+ Other Important Informati...+ Patient Information Sheet+ Pharmacology Review+ Printed Labeling+ Review+ Statistical Review+ Summary Review</div>	Aripiprazole
	<p>← Use the browse tree at the left to browse th</p> <p>To expand/contract a section on the Table of C</p> <p>FDA Approval Package contain the following*:</p> <ul style="list-style-type: none">• Reviews: A review is the basis of FDA's d prepared by FDA drug application review pharmacology, statistics, and microbiolog• Labels: The FDA approved label is the of adverse events (side effects); instructions found inside drug product packaging.• Approval Histories (Administrative Do involving one drug product having a part labeling, a new route of administration, a <p>* = descriptions from USFDA website</p>

03

利用Pharmapendium 进行临床前 及临床信息检索

ParmaPendium支持临床前，临床信息检索

- 毒理/安全数据的检索

- FDA Advisory Committee-AC报告的检索
- QT: 心脏毒理QT间隔延长性趋势的研究

- 药效信息的检索

- 糖尿病替代临床终点信息检索，辅助临床方案决策
- 非小细胞肺癌临床安慰剂组信息检索

- 药代动力学信息检索

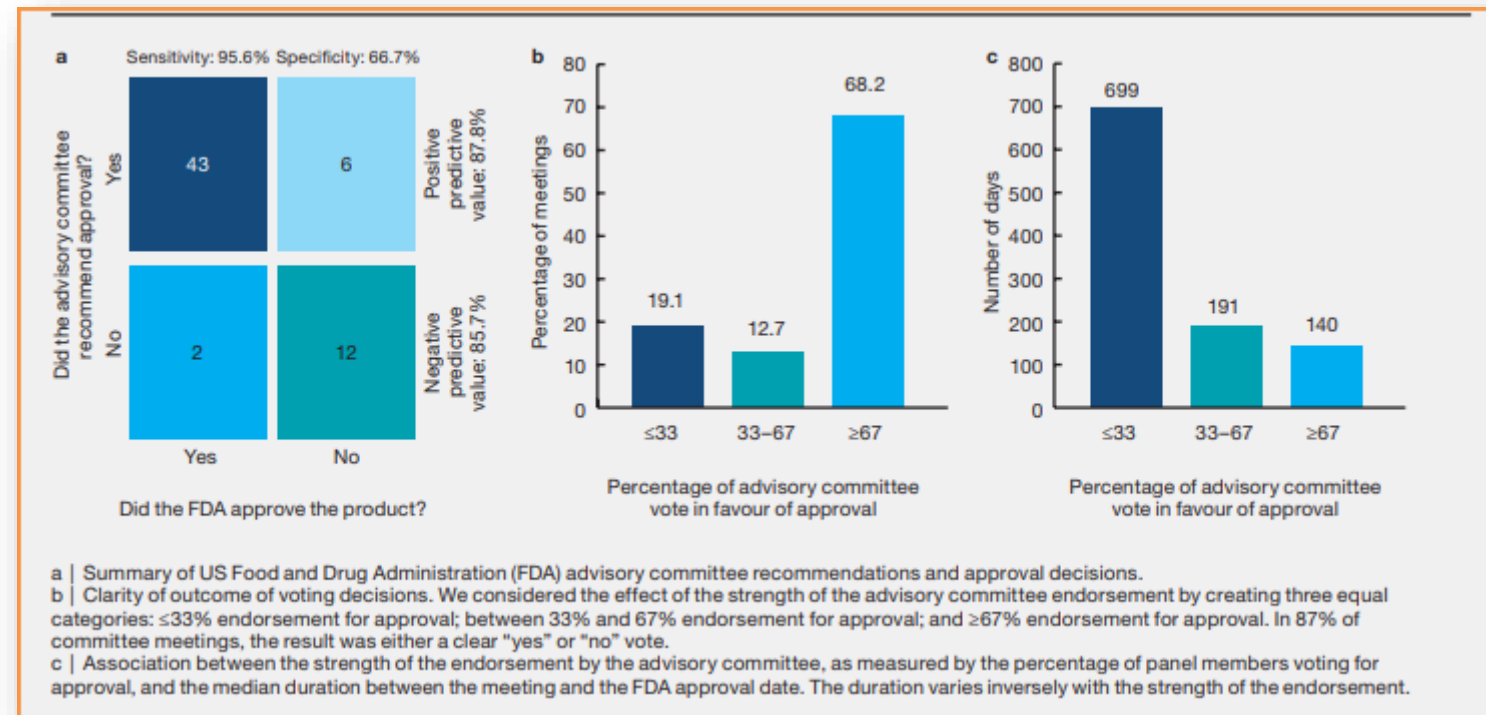
- 同靶点药物血浆蛋白结合率的研究
- 不同种族对临床剂量的影响研究
- 首过代谢相关信息检索与研究

FDA Advisory Committee-AC报告的检索

FDA Advisory Committee Meeting reports-FDA AC 报告

2001-2010 FDA新药上市申请为例

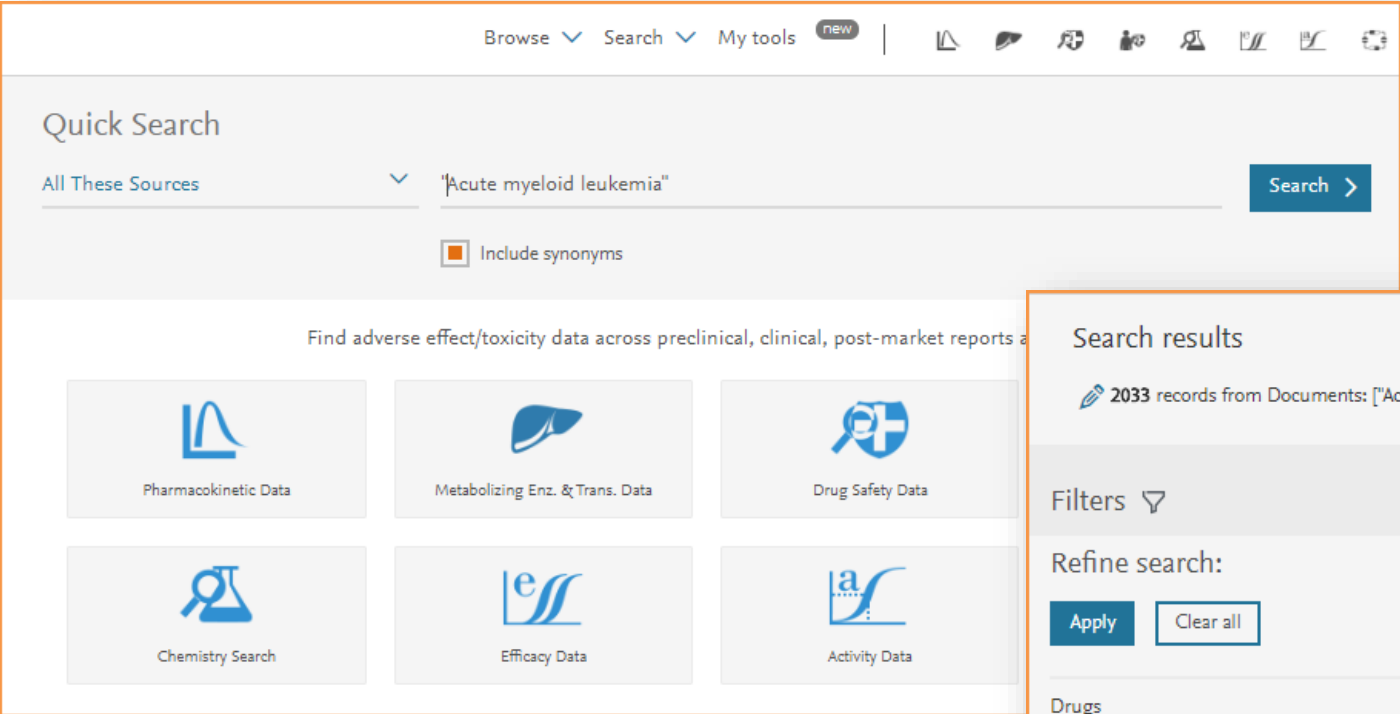
- 在IDN/DNA申请过程中FDA/EMA会参考咨询委员会的意见来决定是否批准申请
- FDA/EMA咨询委员会专家会根据自己的不同见解提出需要解答的问题。
- 通过收集已有审批通过的药物的评审报告，能够参考推测评审委员会可能提出的问题从而提高审批的成功率
- 在FDA官网检索，AC报告并不在approval package中，且只能按年限检索，且一次只能阅读一份报告



https://www.mckinsey.com/~media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx

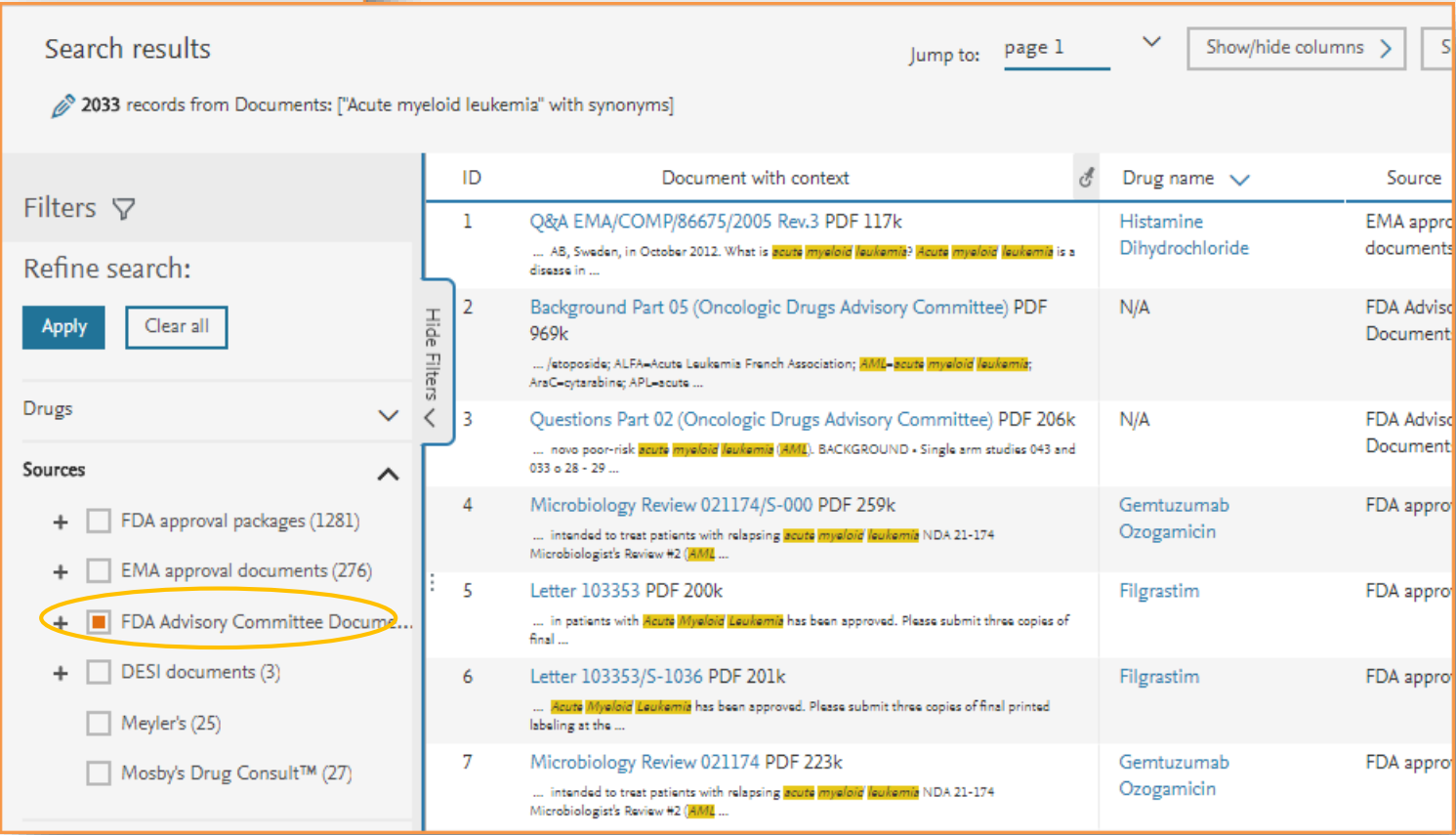
FDA-AC---报告快速检索

➤ 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



1. 直接输入 ‘ “Acute myeloid leukemia” ’ 进行free text检索

2. 结果集中，通过 ‘sources’ 的筛选可以直接找到AC报告



FDA-AERs---上市后副作用监控

➤ 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

+ ☐ DESI documents (3)

☐ Meyler's (25)

☐ Mosby's Drug Consult™ (27)

Years v

+ ☐ Medical Imaging Drugs Advisory Committee

+ ☐ Nonprescription Drugs Advisory Committee

☒ Oncologic Drugs Advisory Committee

☒ 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报告结果集点击即可查看原文结果

➤ 不同咨询委员会的报告可以直接分类得到

➤ 医学影像药物咨询委员会，非处方咨询委员会.....

ID	Document with context	Drug name	Source	Year
1	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 Committee Documents	2017
2	Questions Part 02 (Oncologic Drugs Advisory Committee) PDF 206k ... novo poor-risk acute myeloid leukemia (AML) . 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 acute myeloid leukemia (AML) . 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 acute myeloid leukemia (AML) . 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 AML . Page 25, Myelodysplastic Syndrome/ Acute Myeloid Leukemia . 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 acute myeloid leukemia ; results from Study AML-BFM 2004. Blood 2013;122 ...	N/A	FDA Advisory Committee Documents	2017

FDA-AERs---上市后副作用监控

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

Questions Part 02

115% Go

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

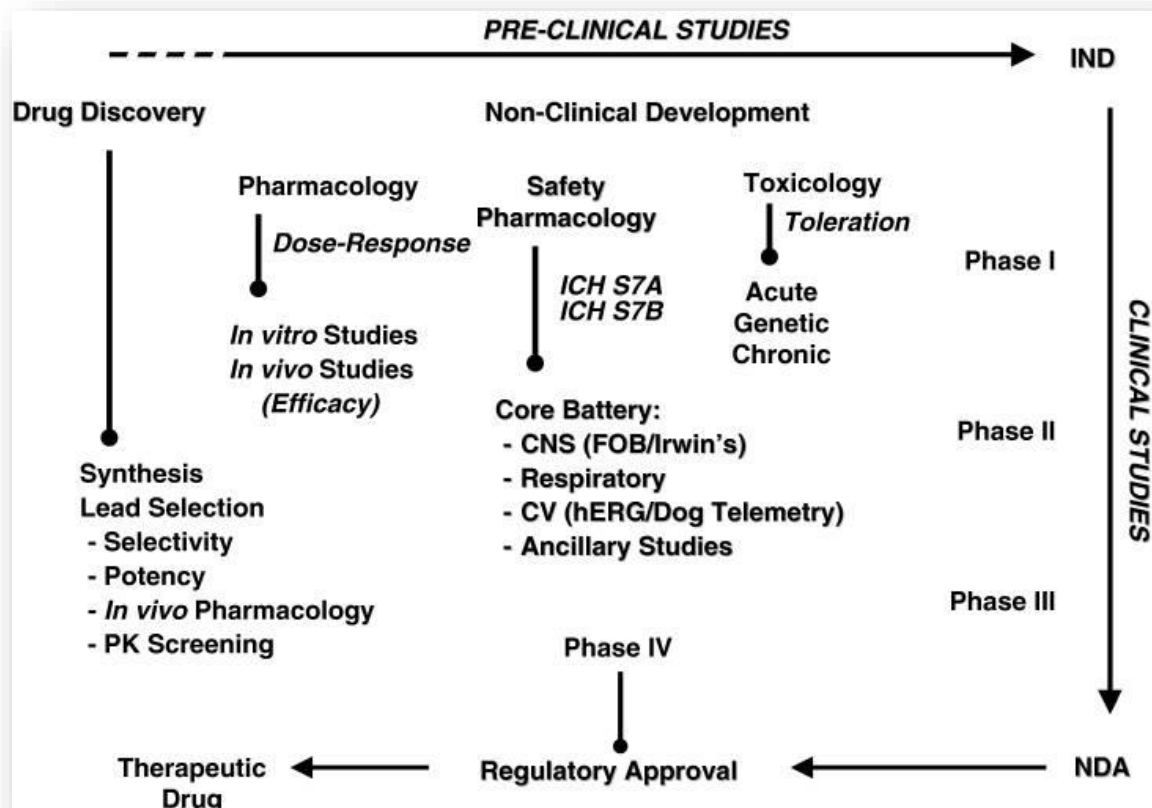
VOTE: Should a randomized study defining the efficacy and safety of laromustine in the population proposed for the indication be completed prior to approval of laromustine?

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

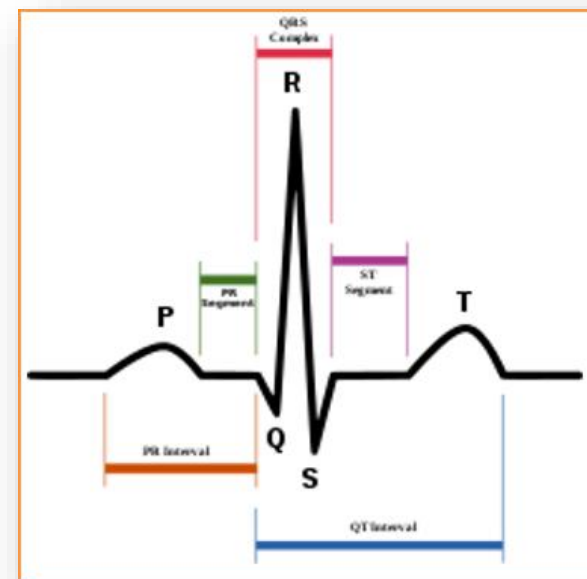
临床前毒理-----QT延长趋势研究

FDA----Safty---临床前毒理研究

➤ 安全药理学：QT 信号通路延长趋势研究



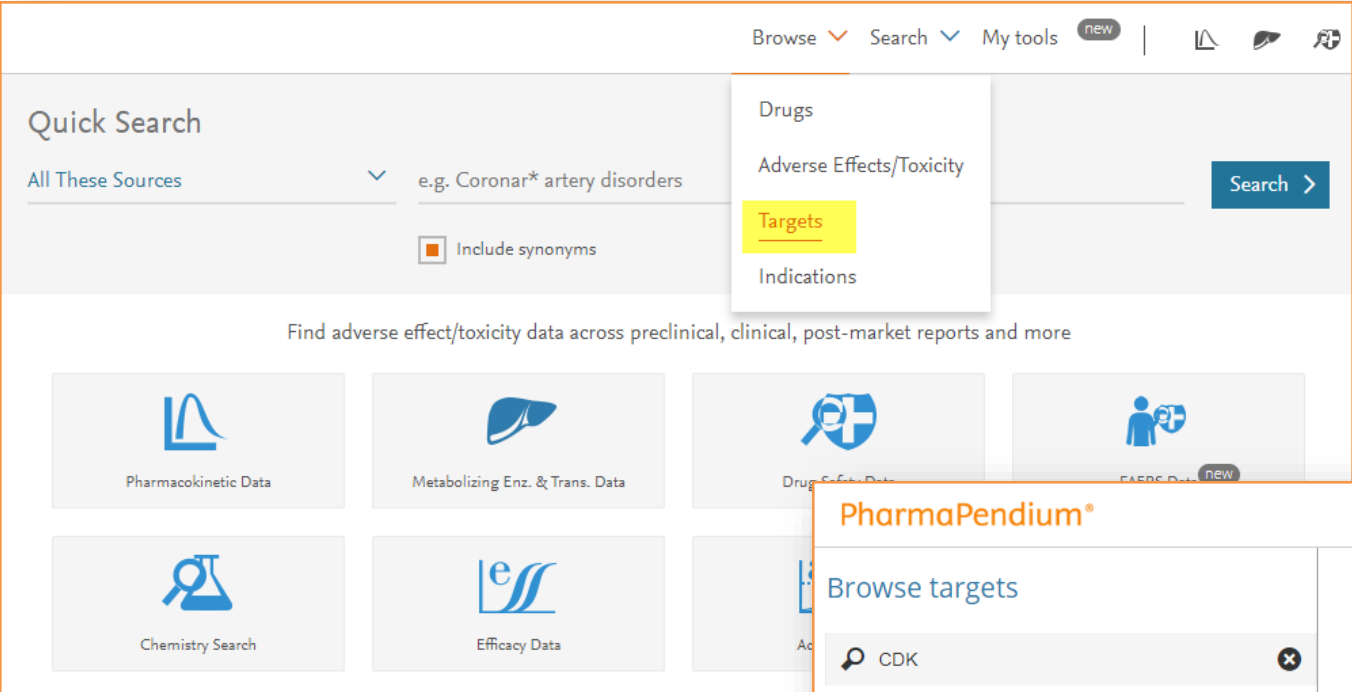
QT interval (QT间隔) 在心脏心电周期中Q信号和T信号的间隔周期是非常重要的检测指标. 它们的时长指标能够指示快速心率失常的潜在风险



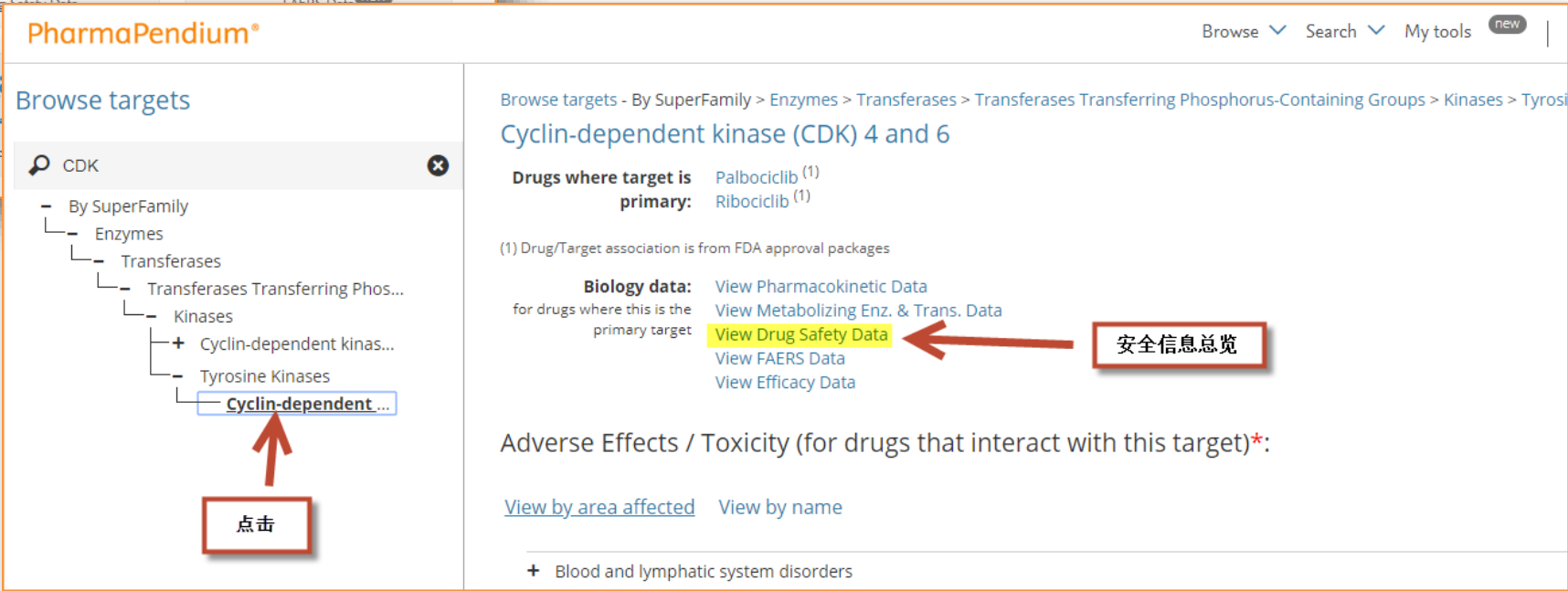
2005年以后, FDA和EMA要求几乎所有的新药都要进行彻底的QT研究, 验证新药分子对于QT interval (间隔) 的影响.

FDA----Safty---临床前毒理研究

➤ 检索，作用于统一靶点的药物对于QT有影响的研究信息（CDK为例）



1. 在检索主界面选择靶点 'target' 检索
2. 在新界面输入 'CDK' 并找到改靶点的总览信息



FDA----Safty---临床前毒理研究

➤ 筛选锁定与靶点对应的做过QT研究的药物信息

1. 在filters筛选器栏，选择对应QT研究选项得到结果
2. 在结果界面选择希望看到的‘临床前’+‘临床’等研究信息
3. 选择对应的结果，查看原文

Filters ▾

Refine search:

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Adverse Effects / Toxicity

- ☐ Blood and lymphatic system disorders (212)
- ☐ Cardiac disorders (10)
- ☐ Eye disorders (41)
- ☐ Gastrointestinal disorders (233)
- ☐ General disorders and administration site c
- ☐ Hepatobiliary disorders (43)
- ☐ Infections and infestations (97)

☒ Investigations (269)

- ☒ Cardiac and vascular investigations (excl...
- ☒ ECG investigations (32)
- ☒ Electrocardiogram QT prolong...
- ☐ Cytogenetic investigations (1)

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Safety data search results

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

[Preclinical Data](#) [Clinical Data](#) [Post-Marketing Reports \(AERS\)](#) [All Data](#)

ID	Drug ▾	Adverse Effect / Toxicity ▾	Species ▾	Dose ▾	Dose Type ▾	Route ▾	Source ▾	Year ▾
1	Palbociclib	Electrocardiogram QT prolonged	Dog	>3 mg/kg	Single	Intravenous	EMA approval document: Assessment Report (Page:23) PDF 4262k	2016
2	Palbociclib	Electrocardiogram QT prolonged	Dog	>10 mg/kg	Single	Intravenous	EMA approval document: Assessment Report (Page:23) PDF 4262k	2016
3	Ribociclib	Electrocardiogram QT prolonged	Dog	20 mg/kg	Single	Oral	FDA approval package document: Approval Package (Page:40) PDF 1644k	2016

FDA----Safty---临床前毒理研究

➤ 直接在原文中参考实验方法和结论

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EMA Approval Package

EMA Approval Package - Palbociclib > Assessment Report

Assessment Report EMA/652627/2016; EMEA/H/C/003853/0000

Search this EMA Package

- + All Authorized Presentations
- + ANNEX I
- Assessment Report
 - 2016-09-15 PDF(4262k)
 - Assessment Report EMA/652627/2016...
- + Marketing Authorization Steps
- + Other Information from EMA
- + Public Assessment Report

Safety pharmacology programme

The potential for palbociclib to cause neurofunctional effects was evaluated in Sprague-Dawley rats following administration of a single oral dose. Decreased exploratory behaviour during the open-field assessment was considered palbociclib-related at 300 mg/kg. Consistent with decreased exploratory behaviour and hypoactivity, a decrease in activity (although not statistically significant) was observed at 300 mg/kg. Mean total distance and number of vertical movements were 19% and 18% less than controls, respectively. Palbociclib had no effect on neurofunction in rats at 30 or 300 mg/kg, but a decrease in locomotor activity was identified at 300 mg/kg.

The potential effect of palbociclib on pulmonary function was assessed following administration of a single intravenous dose to anesthetized Beagle dogs. Two of 4 animals administered palbociclib at 5 mg/kg stopped breathing less than 2 minutes after initiation of drug infusion. Significant increases in minute volume and respiratory rate (0.6- to 4.6-times relative to the controls) were also observed at 4 to 8 minutes postdose and at 18 to 26 minutes postdose at 5 mg/kg. Altogether, a single IV dose of palbociclib in anesthetized dogs at 5 mg/kg caused significant effects on pulmonary parameters, including increases in minute volume and respiratory rate, and decreases in compliance, peak expiratory flow, and tidal volume. The effects were transient, appeared related to peak-plasma concentrations of drug (≥ 2040 ng/mL; ≥ 843 ng/mL unbound, based on fu 0.413 in the dog), and were consistent with respiratory depression.

The potential for palbociclib to cause cardiovascular effects following administration of a single dose was evaluated in conscious Beagle dogs. The data show that single doses of palbociclib were associated with QTc interval prolongation in dogs at ≥ 3 mg/kg where plasma concentrations were ≥ 162 ng/mL (67 ng/mL unbound based on fu of 0.413 in dogs, 4 times clinical C_{max} [17 ng/mL]). Palbociclib also caused increases in QT interval, decreases in HR with a corresponding increase in RR interval, and a modest increase in systolic blood pressure at ≥ 10 mg/kg (mean C_{max} at 10 mg/kg was 140 ng/mL unbound).

The findings in telemetered dog were addressed in the clinic by ECG recordings performed during the Phase 1/2 study 1001, 1002, 1003 and 1010. A PK/PD analysis of the relationship between palbociclib exposure and ECG data was conducted using pooled data from Studies 1001, 1002, and 1003. A positive correlation was observed between QTc and palbociclib concentration. These data are further assessed in the clinical section.

Pharmacodynamic drug interactions

Pharmacological interaction between palbociclib and anti-estrogen agents such as fulvestrant and letrozole has been described above. No additional pharmacodynamic drug interaction studies have been conducted (see

23 of 140

➤ 以动物模型
'dog' 为基础的QT实验研究得出结论，可以在研药物的动物模型选择和条件开发提供参考

FDA----Safty---临床前毒理研究

➤ 同样可以参考临床实验中的QT研发信息

19 records from Safety data: [Palbociclib (0) OR Ribociclib (19)] AND [FDA approval packages (19)] AND [[Electrocardiogram QT prolonged (19)]]

Show/hide columns > Show drugs i

Preclinical DataClinical DataPost-Marketing Reports (AERS)All Data

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
13	Ribociclib	Electrocardiogram QT prolonged	Human	7 days off treatment 600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:19) PDF 1644k	2016
14	Ribociclib	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:80) PDF 1681k	2016
15	Ribociclib	Electrocardiogram QT prolonged	Human	50-1200 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:16) PDF 4058k	2016
16	Ribociclib	Electrocardiogram QT prolonged	Human	600 mg/once a day 21 days, then 7 days off treatment	Repeated	Oral	FDA approval package document: Label (Page:5) PDF 767k	2017
17	Ribociclib	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then	Repeated	Oral	FDA approval package document: Approval Package (Page:15) PDF 2766k	2016

FDA----Safty---临床前毒理研究

➤ 该药的标签中，得到明确的关于Ribociclib的QT毒副作用的描述

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FDA Approval Package - Ribociclib > Label

Label 209092/S-001

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 Information fro...
- + Review

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 serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting 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, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval [see *Clinical Pharmacology* (12.3)].

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 [see *Dosage and Administration* (2.2) and *Drug Interactions* (7.4)].

5 of 17

FDA----Safty---临床前毒理研究

- PP中也能快速便捷的得到，交叉信息。如：想进一步了解存在QT问题的药物，是否还有其他DDI（代谢相关）问题

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Safety data search results

19 records from Safety data: [Palbociclib (0) OR Ribociclib (19)] AND [FDA approval packages (19)] AND [[Electrocardiogram QT prolonged (19)]]

Filters

Refine search:

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Adverse Effects / Toxicity

+ - Investigations (19)

Dose Types

Drugs

Routes of Administration

Sources

+ - FDA approval packages (19)

Years

Preclinical Data Clinical Data Post-Marketing Reports (AERS)

ID	Drug	Adverse Effect / Toxicity	Species
1	Ribociclib	Electrocardiogram QT prolonged	Human
2	Ribociclib	Electrocardiogram QT prolonged	Human
3	Ribociclib	Electrocardiogram QT prolonged	Human
4	Ribociclib	Electrocardiogram QT prolonged	Human
5	Ribociclib	Electrocardiogram QT prolonged	Human

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

Show drugs in

Deselect all

Export All drugs in Excel file (.xls)

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

Selected: 1

☒ Ribociclib

> Show in Pharmacokinetic Data

> Show in Metabolizing Enz. & Trans. Data

> Show in FAERS Data

> Show in Efficacy Data

mg/day for 21 days then 7 days off treatment

400-600 mg/day Repeated Oral

600 mg/day for 21 days then Repeated Oral

Approval Package (Page:59) PDF 1681k

FDA approval package document: Approval Package (Page:18) PDF 4058k

FDA approval package document: Approval Package (Page:39) PDF 1681k

FDA----Safty---临床前毒理研究

Metabolizing Enz. & Transporters search results

141 records from ME&T data: [Ribociclib (141)]

Preclinical Data

Clinical Data

All Data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter
1	Ribociclib	Parent	Ribociclib	Enzyme Substrate (in vivo)	CYP3A(unspecified)
2	Ribociclib	Parent	Ribociclib	Enzyme Substrate (in vivo)	CYP3A4
3	Ribociclib	Parent	Ribociclib	Substrate (in vivo)	Unreported
4	Ribociclib	Parent	Ribociclib	Enzyme Substrate (in vivo)	CYP3A4
5	Ribociclib	Parent	Ribociclib	Enzyme Substrate (in vivo)	CYP3A4

Metabolizing Enz. & Transporters search results

141 records from ME&T data: [Ribociclib (141)]

Preclinical Data

Clinical Data

All Data

ID	Drug	Substance measured	Concomitant	Parameter	Value	Result (qualitative)	Source	Year
1	Ribociclib	PARENT	rifampicin, 600 mg/d, for 14 days	Cmax decrease	81%		FDA approval package document: Label (Page:12) View Full Study PDF 767k	2017
2	Ribociclib	PARENT	rifampicin, 600 mg/d, for 14 days	AUC ratio	0.11 fold		FDA approval package document: Approval Package (Page:28) View Full Study PDF 4058k	2016
3	Ribociclib	PARENT	efavirenz	PK (unspecified)		NO	FDA approval package document: Approval Package (Page:18) View Full Study PDF 2766k	2016

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Approval Package 209092/S-...
- 2016-10-04 PDF(2766k)
Approval Package 209092/S-...
- 2016-10-04 PDF(1681k)
Approval Package 209092/S-...
- 2016-10-04 PDF(4058k)
Approval Package 209092/S-...
- 2016-10-04 PDF(2585k)
Approval Package 209092/S-...

+ Chemistry Review

+ Label

+ Letter

+ Other Important Information fro...

+ Review

FDA Approval Package - Ribociclib > Approval Package

Approval Package 209092/S-000 Part 04

13.3.5 PBPK Analysis

13.3.5.1 Objectives

The main objectives of this review are to 1) evaluate the adequacy of applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the drug-drug interaction (DDI) potential of ribociclib as a victim and a perpetrator of the CYP metabolic pathway; 2) provide a dosing recommendation based on the predicted DDI potential; 3) evaluate the adequacy of the applicant's conclusions regarding the ability of a PBPK to predict the impact of stomach pH on the absorption of ribociclib. To support its conclusions the applicant provided the following PBPK modeling and simulation reports and updates:

- Under study report DMPK R1400619 entitled "Predictions of interactions between LEE011 and typical CYP substrates and perpetrators using Simcyp" [1].
 - A PBPK model using first order absorption and considering the CYP3A auto-inhibition was built and verified using clinical DDI study results.
 - The effects of strong CYP3A inhibitors (ritonavir, ketoconazole), strong CYP3A inducers (rifampicin, carbamazepine), a moderate CYP3A inhibitor (erythromycin), a moderate CYP3A inducer (efavirenz), and a weak CYP3A inhibitor (fluvoxamine) on exposure of ribociclib were simulated. These simulations were performed to support ribociclib dosing recommendations when given in combination with CYP3A modulators not evaluated clinically.
 - The net effects of ribociclib on exposure of a CYP3A probe substrate (midazolam) and a CYP1A2 probe substrate (caffeine) were simulated.
- Under study report DMPK R1600364 entitled "In silico evaluation of the impact of stomach pH on the absorption of LEE011 in humans" [2].
 - A human advanced compartment and transit (ACAT) absorption model and an advanced dissolution, absorption, and metabolism model (ADAM) absorption model were built in ribociclib PBPK models to simulate the impact of stomach pH on absorption of ribociclib in humans.

➤ 跳转原文，通过 ‘text searching’ 快速找到 ‘CYD3A’ 代谢相关的 DDI研究

利用 safety Margin 模型来预测针对某个靶点的药物安全性

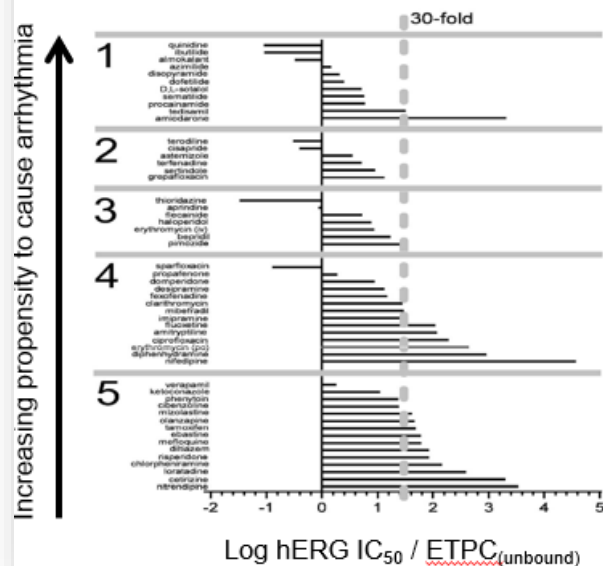
Clinical experience with marketed drugs enables quantitative relationship with in vitro assays

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

$$\text{Safety Margin} = \frac{\text{In vitro IC}_{50}}{ETPC_{(unbound)}}$$

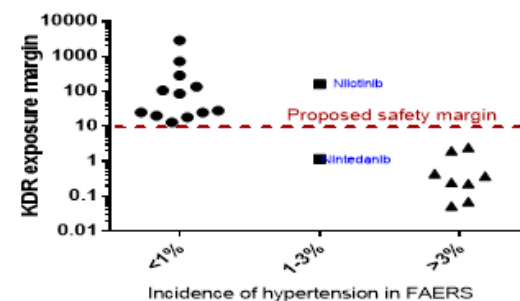
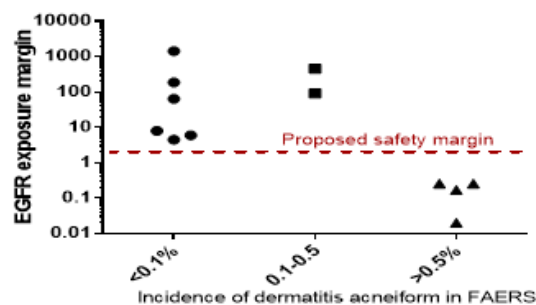
IMPACT: simple, rapid, inexpensive in vitro assay routinely implemented in early disc. Molecules with poor safety margin are de

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



Additional Examples: Setting safety margins for EGFR-dermatitis and KDR-hypertension

- A set of marketed kinase inhibitors were tested in EGFR (HER1) and KDR (VEGFR) biochemical enzymatic assays in house
- The incidence levels of dermatitis acneiform and hypertension respectively were calculated from the number of reports given in FAERS, extracted from PharmaPendium.
 - In each case, the incidence levels were split into three categories estimated to reflect background, medium and high levels of incidence.
- PK information were extracted from PharmaPendium and literature sources
- Suitable safety margins [$IC_{50}/\text{free } C_{max}$] were estimated to be 2 for EGFR and 10 for KDR



药效 (Efficacy) : 糖尿病替代临床终点信 息检索

Efficacy信息检索

➤ 什么是药效 (Efficacy) , 临床终点 (endpoints)

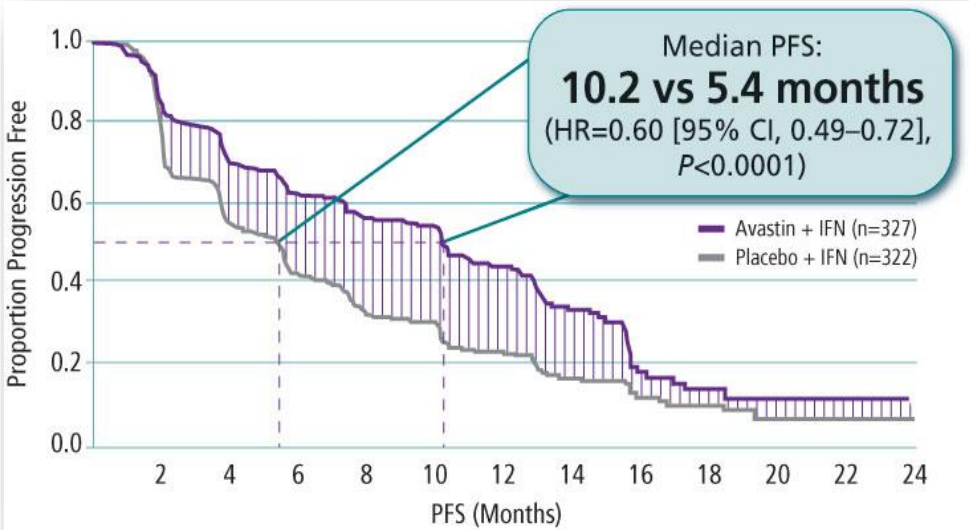
药效 (Efficacy) :

- 在研药物到达研发预期, 相较于以后药物有同等或者更好的效果

临床终点 (endpoints) :

- 几乎所有药物都会安全性问题, 那么病人愿意服用该药物原因: **延长生存期; 改善症状; 减少并发症.....**因此, 临床实验测试终点应该以解决这些问题为主

评价指标之一: 无进展生存期 (PFS)



Progression Free Survival (PFS)

- 临床意义终点:
真实可测的终点: 病人感官, 生存期等可以是客观, 也可以是主观

- 替代临床终点:
被设计能够反映临床意义重点的检测方案, **需要被证实其变化的时候也能反映临床意义终点的变化**, 如图

Validated Surrogate Endpoint	Correlated Clinical Outcome
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) <i>The amount of air that a person can blow out of his or her lungs in 1 second</i>	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load <i>The amount of the human immunodeficiency virus that is present in the blood</i>	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

Efficacy----替代临床终点相关信息检索

➤ 检索，糖尿病的临床替代终点信息 (validated surrogate and unvalidated surrogate)

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... within at least

5

words of one another

... with at least one of the words:

diabetes

... without the words:

☒ Include synonyms

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- Wildcards (* or ?) can be used here

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

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Refine search:

Apply Clear all

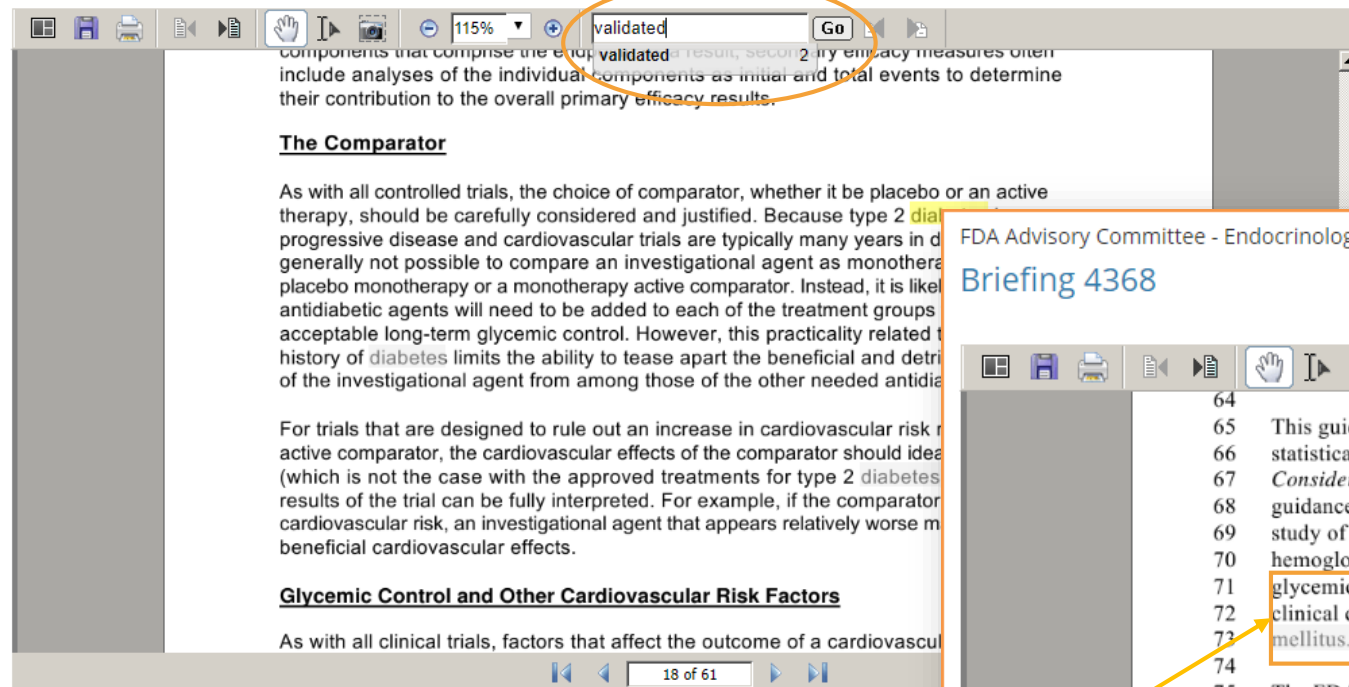
Drugs Sources Years

ID	Document with context	Drug name	Source	Year
1	Assessment Report EMEA/H/C/001247; EMEA/H/C/001243 PDF 756k ... (Important potential risk): Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of ...	Fenofibrate; Pravastatin Sodium	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... diabetes mellitus N Engl J Med. 1999;341:1127-33. 4. Frank RN. Diabetes 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 Diabetes Mellitus ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any diabetic AE Diabetes mellitus Blood glucose increased Glucose tolerance ...	N/A	FDA Advisory Committee Documents	2009
5	Medical/Clinical Review 021366/S-016 PDF 14654k ... Polydipsia 0 0 Diabetes mellitus inadequate control 0 Diabetic ketoacidosis 0 Hyperglycemic hyperosmolar ...	Rosuvastatin Calcium	FDA approval packages	2010

Efficacy---surrogate----原文text searching

FDA Advisory Committee - Endocrinologic and Metabolic Drugs Advisory Committee > 2008-Jul-01-02

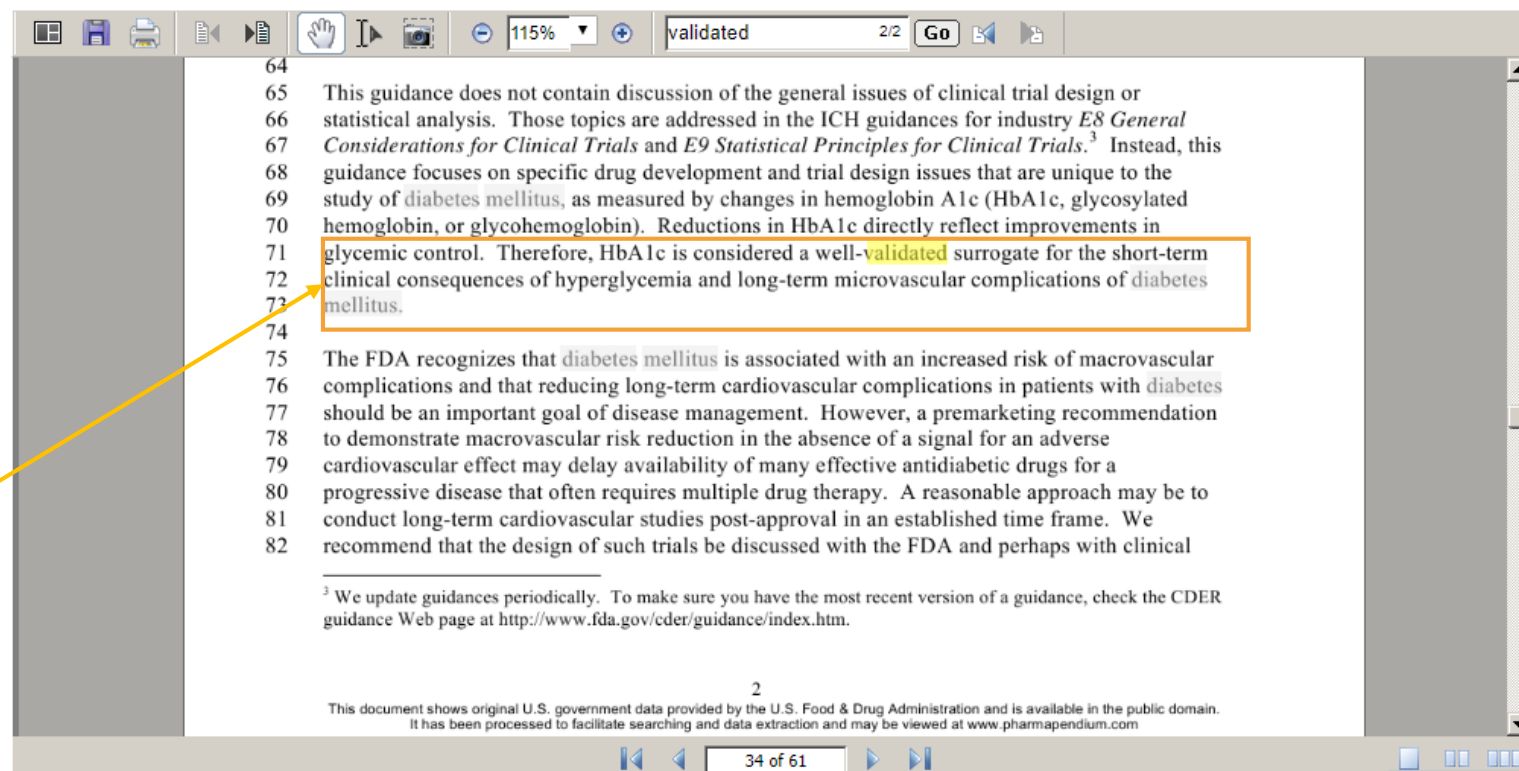
Briefing 4368



- 在原文上直接进行 'text searching' 锁定准确位置

FDA Advisory Committee - Endocrinologic and Metabolic Drugs Advisory Committee > 2008-Jul-01-02

Briefing 4368



HbA1c被认为是well-validated替代
终点.....

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

Efficacy-----unvalidated surrogate信息检索

PharmaPendium®

Browse Search My tools new

Advanced search

Search criteria

Find results

... with **all** the words: surrogate unvalidated

... within at least 5 words of one another

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

... **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.

PharmaPendium®

Browse Search My tools new

Search results

Jump to: page 1 Show/hide columns Show drugs in... Save Export

12 records from Documents: [[surrogate,unvalidated=5] AND (diabetes) with synonyms]

Filters

Refine search:

Apply Clear all

Drugs Sources Years

ID	Document with context	Drug name	Source	Year
1	Briefing 4355 Part 02 (Blood Products Advisory Committee) PDF 466k ... addition, the secondary endpoint of C1INH levels must be considered an unvalidated surrogate endpoint at ...	N/A	FDA Advisory Committee Documents	2008
2	Briefing 4355 Part 01 (Blood Products Advisory Committee) PDF 432k ... unvalidated surrogate endpoint at this time. For the secondary endpoints attack severity and attack duration ...	N/A	FDA Advisory Committee Documents	2008
3	Approval Package 020604/S-040 PDF 2381k ... -related events including new onset diabetes mellitus and diabetic ketoacidosis led to a language upgrade ...	Somatropin, Biosynthetic	FDA approval packages	2011
4	Background Part 17 (Cardiovascular and Renal Drugs Advisory Committee) PDF 2057k ... of 224 Tolvaptan (OPC-41061) NDA 204441 that TKV is an unvalidated surrogate , TKV was chosen as the ...	N/A	FDA Advisory Committee Documents	2013
5	Transcript Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 2384k ... , to understand 16 that concluding that an effect on an unvalidated surrogate will be reasonably ...	N/A	FDA Advisory Committee Documents	2012
6	Background Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 7363k ... deficiency, Diabetes Mellitus , HIV treated with retroviral medications, thyroid disorders, alcohol abuse, and ...	N/A	FDA Advisory Committee Documents	2012

Efficacy—临床终点原文信息快速定位

FDA Advisory Committee

Search this FDA Advisory Coi

2008-05-02 PDF(432k, Briefing 4355 Part 01

2008-05-02 PDF(466k, Briefing 4355 Part 02

2008-05-02 PDF(317k, Briefing 4355 Part 03

2008-05-02 PDF(196k, Briefing 4355 Part 04

2008-05-01 PDF(342k, Minutes 4355

2008-05-01 PDF(247k, Roster 4355

2008-05-02 PDF(360k, Slides 4355 Part 01

2008-05-01 PDF(263k, Slides 4355 Part 01

2008-05-02 PDF(507k, Slides 4355 Part 02

2008-05-01 PDF(684k, Slides 4355 Part 02

2008-05-01 PDF(373k, Slides 4355 Part 03

FDA Advisory Committee - Blood Products Advisory Committee > 2008-May-01-02

Briefing 4355 Part 01

150% unvalidated 1/1 Go

Percent Reduction in HAE Attack Frequency

One explanation for the diversity in responsiveness could be that the dose used was not optimal. At a pre-IND meeting in 2004 FDA recommended phase 2 studies that may have facilitated more optimal dosing for the phase 3 trial. The sponsor declined, citing the rarity of the disease and the difficulty in conducting such phase 2 studies.

Efficacy: Secondary Endpoints

Among the secondary endpoints analyzed by the sponsor were number of drop-outs, average attack severity, average duration of attacks, number of open-label C1INH-nf infusions, change from baseline in C1INH antigenic and functional levels, total number of days of swelling in each study period.

Attack severity and attack duration are related to clinical benefit and appear to be relatively independent. Other secondary endpoints – such as days of swelling and number of open label C1INH infusions – appear not to be independent of the primary endpoint and the secondary endpoints relating to attack duration and severity. In addition, the secondary endpoint of C1INH levels must be considered an **unvalidated** surrogate endpoint at this time.

For the secondary endpoints attack severity and attack duration the following tables give these results:

Attack Severity Scale

... Mild – Events that were usually transient, required no special treatment, and did not interfere with the subject's daily activities.

11 of 20 Feedback

➤二级终点
应当被认为是
unvalidated的
替代终点

Efficacy---临床终点信息总览

- 需要收集 'diabetes' 全部临床终点信息时

The screenshot displays the PharmaPendium website interface. On the left, a 'Quick Search' sidebar is visible with a search bar containing 'e.g. Coronar* artery disorders' and a 'Search' button. Below the search bar, there is a checkbox labeled 'Include synonyms'. The main content area features a grid of icons for different data types: Pharmacokinetic Data, Metabolizing Enz. & Trans. Data, Chemistry Search, and Efficacy Data. The 'Efficacy Data' icon is highlighted with an orange border. To the right, a 'PharmaPendium®' header is shown with navigation links: 'Browse', 'Search', and 'My tools'. Below the header, the 'Efficacy data search' section is displayed, asking the user to 'Show me preclinical & clinical studies for these:'. Under 'Search criteria', there are two columns of options: 'Drugs' (Add drugs by drug class or drug name, Add drugs by primary target or primary target class) and 'Indication Type' (Add indications). Below these, there are sections for 'Species' (Add species), 'Sources' (Add sources), and 'Endpoints' (Add endpoints). The 'Endpoints' section is highlighted with an orange border.

Quick Search

All These Sources ☐ e.g. Coronar* artery disorders ☐ Include synonyms

Find adverse effect/toxicity data across preclinical, clinical

Pharmacokinetic Data

Metabolizing Enz. & Trans. Data

Chemistry Search

Efficacy Data

PharmaPendium®

Browse My tools

Efficacy data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

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

Indication Type

- + Add indications

Species

- + Add species

Sources

- + Add sources

Endpoints

- + Add endpoints

Efficacy---临床终点信息总览

- 只需要输入 'hba1c' 搜集, 并选择与 'diabetes' 相关的临床终点信息即可, 快捷方便

Add endpoints

Search: hba1c

- ☐ Mean HbA1c
- ☐ Mean Ratio to baseline in HbA1c
- ☒ Diabetes
 - ☒ Clinical chemistry
 - ☐ Fasting plasma glucose (FPG) and Glycated hemoglobin (HbA1c)
 - ☐ %patients achieved and maintained control of blood glucose and Hb...
 - ☒ Glycated hemoglobin (HbA1c)
 - ☒ % of patients who had a fall in glycated hemoglobin A1c (HbA1c) of 1.0
 - ☒ % of subjects achieving an HbA1c level < 7.0%
 - ☒ % of subjects who achieved target HbA1c levels of <7.0%
 - ☒ % of subjects with HbA1c level 7.0% to 7.5%
 - ☒ % of subjects with HbA1c level 7.5% to 8%
 - ☒ % of subjects with HbA1c level 8% to 8.5%
 - ☒ % of subjects with HbA1c level 8.5% to 9%
 - ☒ % of subjects with HbA1c level 9% to 9.5%
 - ☒ % of subjects with HbA1c level 9.5% to 10%

Search on:

Endpoints

x Diabetes, Clinical chemistry, Glycat...

Efficacy---临床终点信息总览

- 对感兴趣的内容进行进一步的筛选：如，找到phase II, III等明确的临床终点信息

Efficacy data search results

39351 records from Efficacy data: [Glycated hemoglobin (HbA1c) (39351)]

Filters ▾

Refine search:

Apply Clear all

- Drugs ▾
- Routes of Administration ▾
- Mono/Combination ▾
- Sample size (#N) ▾
- Indication Type ▾
- Endpoints ▾
- Phase ▾
- Data provider ▾

Preclinical Data		Clinical Data				
ID	Drug ▾	Study Number ▾	Phase ▾	Mono/Combination ▾	Study Design ▾	Species ▾
1	Acarbose	642.0	Not specified	Monotherapy	placebo controlled double blind study	Human
2	Acarbose	D95-020	Not specified	Combination	31-week, multi-center, randomized, double-blind, placebo-controlled, two arm, parallel-group comparison study	Human
3	Acarbose	96/004	Not specified	Combination	double blind placebo-controlled study	Human
4	Acarbose	626.0	Not specified	Combination	12 month study	Human
5	Acarbose	633.0	Not specified	Monotherapy	double blind dose-response study	Human
6	Acarbose	642.0	Not specified	Monotherapy	randomized, double-blind, multi-center Italian placebo-controlled study	Human
7	Acarbose	626.0	Not	Combination	four arm double blind adjunct study	

Feedback

Efficacy---临床终点信息总览

Efficacy data search result

39351 records from Efficacy data:

☒ II (990)

☒ II/III (370)

☒ IIb (44)

☒ IIb/III (93)

☒ III (14078)

☒ IIIa (23)

☒ IIIb (615)

☒ IV (4)

☐ Not specified (23134)

Data provider

☐ Literature (22)

☒ Reviewer (15618)

☐ Sponsor (15747)

☐ Unreported (7964)

Preclinical DataClinical Data

ID	Drug	Combination	Study Design	Species	Sex	Age	Indication Type	Indication
1	Canagliflozin	xy	phase 2, placebo-controlled dose-finding	Human	Both	Adult-aged	Diabetes mellitus type 2	Type 2 diabetes m
2	Canagliflozin	xy	phase 2, placebo-controlled dose-finding	Human	Both	Adult-aged	Diabetes mellitus type 2	Type 2 diabetes m
3	Canagliflozin	xy	phase 2, placebo-controlled, dose-finding	Human	Both	Adult-aged	Diabetes mellitus type 2	Type 2 diabetes m
4	Canagliflozin	xy	phase 2, placebo-controlled dose-	Human	Both	Adult-aged	Diabetes mellitus type 2	Type 2 diabetes m

Preclinical DataClinical Data

ID	Drug	PValue	Study Population	Experimental Detail	Data Provider	Source	Year
1	Canagliflozin		LOCF-ITT	baseline	Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
2	Canagliflozin	<0.001	LOCF-ITT		Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
3	Canagliflozin				Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
4	Canagliflozin		LOCF-ITT	baseline	Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
5	Canagliflozin				Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
6	Canagliflozin	<0.001	LOCF-ITT		Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013
7	Canagliflozin	<0.001	LOCF-ITT		Reviewer	EMEA approval document: Assessment Report (Page:41) View Full Study PDF 1815k	2013

Feedback

Efficacy---临床终点信息总览

EMA Approval Package - Canagliflozin > Assessment Report

Assessment Report EMA/374133/2013; EMEA/H/C/002649/0000

A step-down to an assessment of superiority was pre-specified; the upper limit of the 95% CI between CANA 300 mg and glimepiride was $<0\%$, demonstrating superiority for CANA to glimepiride. The HbA1c lowering response to CANA 100 mg was not superior to that of glimepiride in this study. The absolute HbA1c reductions in the three treatment arms were about -0.7% and are considered to be clinically relevant, although the true effect cannot be assessed in the absence of a placebo arm.

The results on the secondary glycaemic endpoints (FPG lowering, proportion of responders) generally supported those on HbA1c. Body weight decreased in the CANA groups compared to a small gain in the glimepiride group. A substudy investigating body composition showed that fat loss contributed significantly to body weight reduction. Glimepiride-subtracted change in systolic blood pressure was -3.48 mm Hg and -4.76 mm Hg for the 100 mg and 300 mg dose, respectively.

Trends in favour of CANA as compared to glimepiride were also shown for measures of beta cell function (HOMA-2%B). Notably, the improvement in HOMA-2%B was numerically superior to glimepiride which acts directly at the beta cell. Reversal of glucotoxicity leading to improved beta-cell function may play a role.

With glimepiride the durability of HbA1c lowering was worse compared to both CANA doses which showed little change through week 52. The waning of effect is known for insulin secretagogues. Durability of the effect of CANA can be further assessed based on data of the long term extension study.

53 of 115

Feedback

PharmaPendium帮助客户在快速收集概览信息的同时，也能很便捷的辅助客户阅读原文中的细节

药效：非小细胞肺癌安慰剂组相关信息检索

Efficacy---安慰剂组临床信息检索

- 在进行临床方案设计和决策时，如何快速根据适应症收集特定的临床经验来辅助决策，提高效率？如：检索已有的NSCLC安慰剂效应相关临床研究

Quick Search

All These Sources ▾ e.g. Coronar* artery disorders

Search >

☐ Include synonyms

Find adverse effect/toxicity data across preclinical, clinical,

Pharmacokinetic Data

Metabolizing Enz. & Trans. Data

Chemistry Search

Efficacy Data

PharmaPendium®

Browse ▾ Search ▾ My tools new

Efficacy data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

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

Indication Type

- + Add indications

Species

- + Add species

Sources

- + Add sources

Endpoints

- + Add endpoints

Search

Efficacy----安慰剂组临床信息检索

Add indications

non small cell lung

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Respiratory and mediastinal neoplasms malignant and unspecified

Non-small cell neoplasms malignant of the respiratory tract cell type specified

Non-small cell lung

Non-small cell lung

☒ Non-small cell lung cancer

☒ Non-small cell lung cancer

☒ Non-small cell lung cancer advanced

☒ Non-small cell lung cancer advanced, anaplastic lymphoma

☒ Non-small cell lung cancer advanced, metastatic

☒ Non-small cell lung cancer advanced, with PD-L1 expression

☒ Non-small cell lung cancer metastatic

☒ Non-small cell lung cancer metastatic, anaplastic lymphoma

☒ Non-small cell lung cancer metastatic, epidermal growth factor receptor

☒ Non-small cell lung cancer stage IV

Search on:

Indication Type

x Non-small cell lung cancer

PharmaPendium®

Browse Search My tools new

Efficacy data search results

26771 records from Efficacy data: [Non-small cell lung cancer (26771)]

Data provider

Sources

Study design

Primary/Secondary

Pathogens

Dose Frequency

Baseline

Placebo

Comparative Group

Study population

Preclinical Data

Clinical Data

ID	Drug	Study Number	Phase	Mono/Combination	Study Design
1	Afatinib Dimaleate	1200.22 (LUX-Lung 2)	II	Monotherapy	A Phase II, non-randomized, single arm, open-label, uncontrolled trial
2	Afatinib Dimaleate	1200.22 (LUX-Lung 2)	II	Monotherapy	A Phase II, non-randomized, single arm, open-label, uncontrolled trial
3	Afatinib Dimaleate	1200.22 (LUX-Lung 2)	II	Monotherapy	A Phase II, non-randomized, single arm, open-label, uncontrolled trial
4	Afatinib Dimaleate	1200.22 (LUX-Lung 2)	II	Monotherapy	A Phase II, non-randomized, single arm, open-label, uncontrolled trial
5	Afatinib Dimaleate	1200.72	II	Monotherapy	A Phase II, non-randomized, open-label, uncontrolled, additional trial
6	Afatinib Dimaleate	1200.22 (LUX-Lung 2)	II	Monotherapy	A Phase II, non-randomized, single arm, open-label, uncontrolled trial

➤ 结果集中直接筛选 ‘安慰剂’ 得到以适应症为基础的安慰剂效应研究总览表

Efficacy

Efficacy data search results

2792 records from Efficacy data: [Non-small cell lung cancer (2792)] AND [Placebo (2792)]

Preclinical Data

Clinical Data

ID	Drug	Study Number	Phase	Mono/Combination	Study Design	Species
1	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label,	Human
2	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III			
3	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III			
4	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III			
5	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III			
6	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III			

➤ 可以进行跟多的细节筛选：筛选FDA-approval中的review report可以查看原文获得更多的细节，有助于决策

Efficacy data search results

124 records from Efficacy data: [Non-small cell lung cancer (124)] AND [Reviewer (124)] AND [Placebo (124)] AND [FDA approval packages (124)]

Preclinical Data

Clinical Data

ID	Drug	PValue	Study Population	Experimental Detail	Data Provider	Source	Year
1	Afatinib Dimaleate	<0.0001			Reviewer	FDA approval package document: Medical/Clinical Review (Page:9) View Full Study PDF 406k	2013
2	Bevacizumab		ITT	Sensitivity Analysis 1	Reviewer	FDA approval package document: Approval Package (Page:44) View Full Study PDF 5688k	2006
3	Bevacizumab		ITT	Sensitivity Analysis 3	Reviewer	FDA approval package document: Approval Package (Page:44) View Full Study PDF 5688k	2006
4	Bevacizumab		ITT	Sensitivity Analysis 2	Reviewer	FDA approval package document: Approval Package (Page:44) View Full Study PDF 5688k	2006

Efficacy

FDA Approval Package - Afatinib Dimaleate > Summary Review

Summary Review 201292/S-000

BI proposed the following indication [REDACTED]

[REDACTED] In this trial, patients randomized to afatinib experienced longer PFS (HR 0.38, $p < 0.0001$ per independent review) with median PFS times of 3.3 months in the afatinib arm compared to 1.1 months for the placebo arm. In addition, the overall response rate was statistically significantly higher (7.4% vs. 0.5%, $p = 0.0071$), how considered clinically important.

3. CMC/Biopharmaceutics

CMC and Biopharmaceutics

I concur with the conclusions reached by the chemistry and biopharm regarding the acceptability of the manufacturing of the drug product that there are no outstanding CMC issues that preclude approval.

Afatinib (free base) is a new molecular entity which is chemically synthesized afatinib dimaleate. The drug substance [REDACTED] is [REDACTED] generated during synthesis. The synthetic process was optimized due to potential impurities and degradants were identified and are appropriate release specification and analytical procedures are described in sufficient for their intended uses; since the methods were not novel or complex

12 of 55

➤ 安慰剂组与非安慰剂组的临床结果对比

FDA Approval Package - Afatinib Dimaleate > Summary Review

Summary Review 201292/S-000

The study population demographics were female (59%), median age of 61 years, baseline ECOG performance status of 0 or 1 (92%), either White (33%) or Asian (66%). All patients were required to have received prior platinum-containing regimen, 60% had 1 line and 39% had 2 lines of prior chemotherapy for metastatic disease. All patients had received prior EGFR TKI therapy, consisting of erlotinib (55%), gefitinib (40%) or both (5%).

The trial failed to meet its primary endpoint, of demonstration of improved survival, with a median survival of 10.8 months for afatinib-treated patients and 12.0 months for patients in the placebo arm. Therefore, the effects on PFS cannot be considered statistically significant and is of unclear clinical importance with an improvement in median PFS time of 2.2 months for afatinib (median PFS 3.3 months) as compared to placebo (median PFS 1.1 months). Similarly, the higher response rate observed with afatinib is not clinically meaningful as it remains less than 10%.

- LUX-5: This was an open-label, randomized, multicenter trials conducted in 1154 patients with patients with unresectable or metastatic NSCLC. Eligibility criteria were similar to those in the LUX-1 trial. All patients received afatinib 50 mg daily; at the time of disease progression, the subgroup deemed to have clinical benefit (without disease progression for ≥ 12 weeks) received afatinib 40 mg daily plus paclitaxel or to receive investigator's choice chemotherapy.

43 of 55

Feedback

➤ 临床结果失败实验的描述, 辅助在研药物的方案设计与决策

药代动力学：动物模型相关信息检索，血浆蛋白结合率

➤ FDA关于临床前动物模型选择的指导意见

VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

After the HEDs have been determined from the NOAELs from all toxicology studies relevant to the proposed human trial, the next step is to pick one HED for subsequent derivation of the MRSD. This HED should be chosen from the most appropriate species. In the absence of data on species relevance, a default position is that the most appropriate species for deriving the MRSD for a trial in adult healthy volunteers is the most sensitive species (i.e., the species in which the lowest HED can be identified).

Factors that could influence the choice of the most appropriate species rather than the default to the most sensitive species include: (1) differences in the absorption, distribution, metabolism, and excretion (ADME) of the therapeutic between the species, and (2) class experience that may indicate a particular animal model is more predictive of human toxicity. Selection of the most appropriate species for certain biological products (e.g., human proteins) involves consideration of various factors.

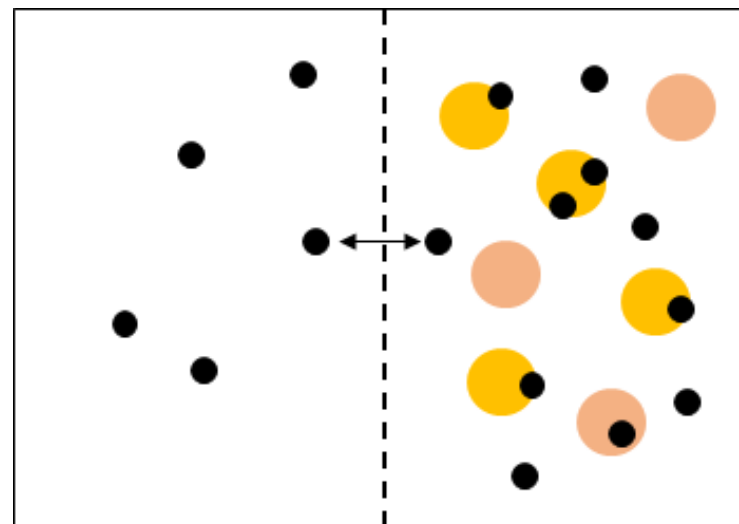
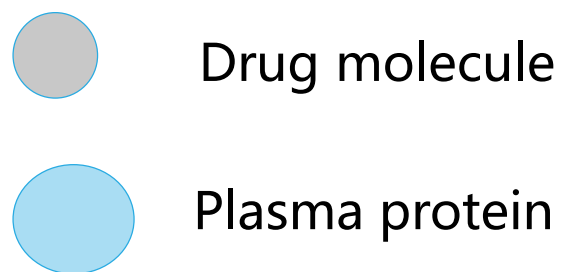
relevant receptor
Preclinical Studies

When determining

distribution, and elimination parameters will not be known for humans. Comparative metabolism data, however, might be available based on *in vitro* studies. These data are

Safety assessment studies that reliably predict hazards of various drugs and other chemicals to human beings or other species "of concern" can be achieved only through selection of appropriate species for study. Thus, identification of laboratory animal species that absorb, distribute, metabolize, and eliminate xenobiotics in ways similar to those in human beings or the other species "of concern" is essential for rational research on the safe use of toxicants in and around these species.

- 蛋白结合: 该指标是药代动力学需要测试的重要指标。药物常常会与血浆蛋白结合, 结合之后将不在具有治疗作用, 而不同动物的血浆蛋白结合率是不一样的。因此, 在临床前实验, 动物模型的选择时, 上市药物的动物模型数据能够辅助决策。



Pharmacokinetic

- 检索同一靶点 (histon deacetylase) 相关药物的不同种属的血浆蛋白结合率

The screenshot displays the PharmaPendium website interface. On the left, a 'Quick Search' sidebar is visible with a search bar containing 'e.g. Coronar* artery disorders' and a 'Search >' button. Below the search bar, there is a checkbox labeled 'Include synonyms'. The main content area is titled 'Pharmacokinetic data search' and includes a subtitle 'Show me preclinical & clinical studies for these:'. Under the 'Search criteria' section, there are two options: 'Add drugs by drug class or drug name' and 'Add drugs by primary target or primary target class', which is highlighted in yellow. To the right of the search criteria, there are sections for 'Parameter ranges', 'Species', and 'Sources', each with a '+' button to add new entries. An orange arrow points from the text '在药代模块当中便捷的进行靶点检索' to the highlighted search criterion.

Quick Search

All These Sources ☐ e.g. Coronar* artery disorders ☐ Include synonyms

Find adverse effect/toxicity data across

Pharmacokinetic Data

Metabolizing Enz. & Trans. Data

Chemistry Search

Efficacy Data

PharmaPendium®

Browse My tools

Pharmacokinetic data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

+ Add drugs by drug class or drug name

+ Add drugs by primary target or primary target class

Parameter ranges

+ Add parameter ranges

Species

+ Add species

Sources

+ Add sources

➤ 在药代模块当中便捷的进行靶点检索

Pharmacokinetic data search results

3160 records from PK Data: [Belinostat (372) OR Panobinostat Lactate (1886) OR Romidepsin (902)]

Filters

Refine search:

Apply

Clear all

Parameter ranges

+

☐

Absorption (1083)

-

☐

Binding (100)

-

☒

Protein binding (100)

☐

Fu (16)

☐

Plasma protein binding ...

☒

Serum protein binding ...

+

☐

Biotransformation (164)

+

☐

Distribution (907)

+

☐

Elimination (906)

Preclinical Data

Clinical Data

All Data

ID	Drug	Species	Study Group	Dose	Route
1	Belinostat	Dog		50 mg/kg/day	Intravenous
2	Belinostat	Rat		25 mg/kg/day	Intravenous
3	Belinostat	Dog		25 mg/kg/day	Intravenous
4	Belinostat	Rat		25 mg/kg	Intravenous
...					
		Rat		25 mg/kg/day	Intravenous
6	Belinostat	Dog		50 mg/kg	Oral
7	Belinostat	Dog		50 mg/kg/day	Intravenous

Hide Filters

Parameter value

Above

below

%

- 结果集中，快速的筛选出血清蛋白结合的临床前和临床数据

Pharmacokinetic

通过 ‘给药剂量’ 排序

➤ 通过 ‘临床前’ + ‘临床’ 数据对比发现，在 ‘剂量’ 相同的情况下血清结合率也有较大的差异，因此在参考在研药物的临床前实验时，可以进行参考。**要看细节时，可以直击原文**

Pharmacokinetic data search results

24 records from PK Data: [Belinostat (0) OR Panobinostat Lactate (0) OR Romidepsin (24)] AND [Serum protein binding (24) %]

Preclinical Data Clinical Data All Data

ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value	SD	t
1	Romidepsin	Human			In Vitro	serum protein binding	93.55 %	0.12	
2	Romidepsin	Human			In Vitro	serum protein binding	94.53 %	0.25	
3	Romidepsin	Dog		50 ng/mL	In Vitro	serum protein binding	87.7 %	0.4	
4	Romidepsin	Rat		50 ng/mL	In Vitro	serum protein binding	40.81 %	0.89	
5	Romidepsin	Human	healthy	50-1000 ng/mL	In Vitro	serum protein binding	94.0% - 95.0%		
6	Romidepsin	Human		50-1000 ng/mL	In Vitro	serum protein binding	94.0% - 95.0%		
7	Romidepsin	Human		50-1000 ng/mL	In Vitro	serum protein binding	≥82.0%		

Pharmacokinetic

Pharmacology Review 022393/S-000 Part 01

Figures in parentheses represent free fraction (%).

In vitro binding of FR901228 to human serum proteins at 500 ng/mL (% bound)

Protein	Conc.	Protein binding of FR901228 (%)
Albumin	40mg/mL	19.91±0.41 (80.09±0.41)
α_1 -AGP	1mg/mL	93.51±0.51 (6.49±0.51)

Mean±S.E., n=3

Figures in parentheses represent free fraction (%).

Tables excerpted from sponsor's package)

Study title: Non-clinical pharmacokinetics: *in vitro* transfer of FR901228 to blood cells in rats, dogs and humans

Key study findings:

- Blood to plasma concentration ratios were less than 1 and nearly constant in rats, dogs and humans from 50 to 5000 ng/mL romidepsin.
- The percent of romidepsin that was transferred from plasma to blood cells was $\leq 25\%$ in rats, $\leq 12\%$ in dogs and $\leq 9\%$ in humans.

Study no.: CRD040012

Volume #, and page #: Electronic submission, Module 4

Conducting laboratory and location:

Date of study initiation: May 8, 2003

GLP compliance: No

QA reports: No

49

56 of 88

➤ 关键性研究的结果的获得

➤ 通过PP特有的 '原文 text searching' 快速获得更多的 'key findings'

Pharmacology Review 022393/S-000 Part 01

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Distribution Studies				
Route	Species	Dose (mg/kg)/Concentration (ng/mL)	Design	Significant findings
<i>in vitro</i>	rat, dog, human	50, 500, 1000, 5000	protein binding study in serum and with human serum proteins	-protein binding was independent of romidepsin concentration up to 500 ng/mL -protein binding was higher in serum from dogs (86%) and humans (94%) than in rats (37%) at 500 ng/mL romidepsin -romidepsin bound better to α_1 -AGP (93%) than to albumin (20%)
<i>in vitro</i>	rat, dog, human	50, 500, 1000, 5000	plasma to blood cell transfer	-blood:plasma ratios < 1 in rats, dogs and humans at ≥ 5000 ng/mL -transfer from plasma to blood cells was $\leq 25\%$ in rats, $\leq 12\%$ in dogs and $\leq 9\%$ in humans
IV	Rat	0.3	organ distribution and excretion of ^{14}C -romidepsin following IV injection	-romidepsin and/or metabolites were widely distributed - C_{max} was highest in kidney, urinary bladder, jejunum, liver and adrenal glands - T_{max} within 5 minutes postdose in all tissues except ileum -primary route of elimination occurred through bile (66% at 48 h postdose), with less occurring through urine (20% at 48 h postdose) after IV administration.
Metabolism Studies				
Route	Species	Dose (mg/kg)/Concentration (ng/mL)	Design	Significant findings
<i>in vitro</i> IV	rat, human	60 μM (microsome incubations);	metabolism of ^{14}C -romidepsin <i>in vitro</i> by liver microsomes and <i>in vivo</i> following IV	-28 metabolites were identified -M1-M14 were produced by rat and human microsomes <i>in vitro</i> -M15-M17 were isolated from rat bile <i>in</i>

73 of 88

Feedback

药代信息检索：种族对与同类型药物给药剂量的影响

Pharmacokinetic—种族对剂量的影响

➤ 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**

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf>

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002842.pdf

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

Quick Search

All These Sources

e.g. Coronar* artery disorders

☐ Include synonyms

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

Pharmacokinetic Data

Metabolizing Enz. & Trans. Data

Drug Safety Data

Chemistry Search

Efficacy Data

Activity Data

Browse

Search

My tools

new

Drugs

Adverse Effects/Toxicity

Targets

Indications

Search

PharmaPendium®

Browse drugs

antineoplastics, monoclonal antibodies

Antineoplastics

Antineoplastics, monoclonal antibod...

Browse drugs - Antineoplastics

Antineoplastics, monoclonal antibodies

Drugs:

Ado-Trastuzumab Emtansine

Alemtuzumab

Atezolizumab

Avelumab

Bevacizumab

Blinatumomab

Brentuximab Vedotin

Catumaxomab

Cetuximab

Daratumumab

... view all ...

Biology data:

View Pharmacokinetic Data

View Metabolizing Enz. & Trans. Data

View Drug Safety Data

View FAERS Data

View Efficacy Data

View Activity Data

Primary targets:

CD19 Antigen (2)

CD20 Antigen (2,4)

CD3 Antigen (2)

CD33 Antigen (3,4)

CD38 antigen (2)

CD52 Antigen (4)

EGFR Receptor 2 Protein (HER2) (2,4)

Epidermal Growth Factor (EGFR) Receptors (1,2)

ErbB1 (2,4)

Glycolipid GD2 (2)

... view all ...

➤ 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

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

PharmaPendium®

Pharmacokinetic data search results

8043 records from PK Data: [Antineoplastics, monoclonal antibodies (8043)]

Filters

Refine search:

Apply

Clear all

Parameter ranges

Drugs

Routes of Administration

Sources

Study Group

Radiolabelled

Metabolites/Enantiomers

Concomitant

Tissue specific

Years

Parameter ranges

Absorption (3250)

Bioavailability (4)

Concentrations (2890)

C (314)

Cavg (138)

☒ Cmax (1536)

Cmin (902)

Time values (356)

Browse

Search

My tools

Show/hide columns

Show drugs in...

Save

Export

Study Group	Dose	Route	Parameter	Parameter Value	SD	t
Unreported	Intravenous	CLt(antibody-drug conjugates)	0.68 L/d			
Unreported	Intravenous	T1/2(conjugate (ADC))	4.0 d			

➤ 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]

Preclinical Data

Clinical Data

All Data

ID	Drug	Species	Study Group	Dose
1	Panitumumab	Human	advanced solid tumors	0.75 mg/kg
2	Panitumumab	Human	advanced solid tumors	1 mg/kg
3	Panitumumab	Human	advanced solid tumors	1.5 mg/kg
4	Panitumumab	Human	advanced solid tumors	2 mg/kg
5	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg
6	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg
7	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg

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)

Source

FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page: View Full Study PDF 7352k)

FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page: View Full Study PDF 7352k)

FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page: View Full Study PDF 7352k)

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PharmaPendium®

Pharmacokinetic data search results

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Filters

Refine search:

Apply

Clear all

Parameter ranges

Drugs

Routes of Administration

Sources

Study Group

Radiolabelled

Metabolites/Enantiomers

Concomitant

Tissue specific

Years

Parameter ranges

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Bioavailability (4)

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Time values (356)

Browse

Search

My tools

Show/hide columns

Show drugs in...

Save

Export

Study Group	Dose	Route	Parameter	Parameter Value	SD	t
Unreported	Intravenous	CLt(antibody-drug conjugates)	0.68 L/d			
Unreported	Intravenous	T1/2(conjugate (ADC))	4.0 d			

➤ 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

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Preclinical Data

Clinical Data

All Data

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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)

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☒ t

☒ Concomitant

☐ Comments

☒ Source

☒ Year

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> Export as Excel document (.xlsx)

> Export as tab delimited (.tsv)

> Export as comma delimited (.csv)

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FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page: View Full Study PDF 7352k)

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PharmaPendium®

Pharmacokinetic data search results

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Refine search:

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Parameter ranges

Drugs

Routes of Administration

Sources

Study Group

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Metabolites/Enantiomers

Concomitant

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Search

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Export

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3	Panitumumab	Human	advanced solid tumors	1.5 mg/kg
4	Panitumumab	Human	advanced solid tumors	2 mg/kg
5	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg
6	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg
7	Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg

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

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☒ t

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FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page: View Full Study PDF 7352k)

Pharmacokinetic---导出结果规整便于分析

- 导出结果不难发现，在剂量相同的情况下，亚洲人种的帕尼单抗的血药浓度呈现了较大的差异，为在研药物的临床实验的方案设计提供参考

[illegible]

Pharmacokinetic---原始文献查看

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

13/37 Go

of arithmetic mean values expressed as a percentage
Study 20030138 for the 2.5 mg/kg QW and Study 20030251 for the 6 mg/kg Q2W.
Source: Intravenous/Debasement/Development/Development/MS 954 -
ABX-EGF/Preclinical Non-Study Specific/PK/MS/Development/Development/Supporting data/Intravenous vs

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

This document shows original U.S. government data provided by the U.S. Food & Drug Administration and is available in the public domain. It has been processed to facilitate searching and data extraction and may be viewed at www.pharmapendium.com

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

64 of 133

➤ 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

12/37 Go

2.5 mg/kg QW 6 mg/kg Q2W

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

2.3.1.4 Body Weight

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)

30 of 133

Feedback

药代动力学：检索血浆结合率<1% 且能抑制CYP3A4 药物相关信息

Pharmacokinetic—按条件设置参数

➤ 检索血清结合率 (serum binding) <1%同时又对CYP3A4 (肝细胞首过代谢酶) 有抑制的药物及其参数信息

The screenshot displays a web-based search interface for drug data. The main section is titled "Quick Search" and includes a search bar with the text "e.g. Coronar* artery disorders" and a "Search >" button. Below the search bar is a checkbox labeled "Include synonyms". A secondary line of text reads "Find adverse effect/toxicity data across preclinical, clinical, post-market reports and more". Below this are four category tiles: "Pharmacokinetic Data" (highlighted with an orange box), "Metabolizing Enz. & Trans. Data", "Chemistry Search", and "Efficacy Data".

An overlay dialog box titled "Add parameter ranges" is open. It shows a tree structure under the "serum" category with the following options:

- Binding
 - Protein binding
 - ☒ Serum protein binding
- Distribution
 - Permeation
 - ☐ Blood/serum ratio
 - ☐ CSF/serum ratio
 - ☐ Milk/serum ratio

On the right side of the dialog, the "Search on:" section is titled "Parameter ranges" and shows a search filter for "x Serum protein binding" with input fields for "Above" and "below 1". The "below 1" field is circled in orange, and the text "设置参数<1" (Set parameter <1) is written next to it.

Pharmacokinetic---快速分类出代谢数据

PharmaPendium®

Browse Search My tools

Pharmacokinetic data search results

74 records from PK Data: [Serum protein binding (74) to 1 %]

Preclinical Data Clinical Data All Data

ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value
1	Amikacin Sulfate	Human	Unreported			serum protein binding	0.0% - 11.0%
2	Amikacin Sulfate	Human	Unreported			serum protein binding	0.0% - 11.0%
3	Amikacin Sulfate	Human	Unreported			serum protein binding	0.0% - 11.0%
4	Bisoprolol Fumarate (14C-labelled)	Human	Unreported			serum protein binding	0.0 %
5	Bisoprolol Fumarate	Human	<=5 ug/mL	In Vitro		serum protein binding	0.0 %
6	Bisoprolol Fumarate	Human	<=5 ug/mL				
7	Bisoprolol Fumarate (14C-labelled)	Human	Unreported				
8	Drospirenone; Ethinyl Estradiol	Human	Unreported				
9	Drospirenone; Ethinyl Estradiol	Human	Unreported				

Show drugs in

Deselect all

Export All drugs in Excel file (.xls)

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

Selected: 12

☒ Amikacin Sulfate

☒ Bisoprolol Fumarate

☒ Drospirenone; Ethinyl Estradiol

☒ Famciclovir

☒ Gadodiamide

> Show in Metabolizing Enz. & Trans. Data

> Show in Drug safety Data

> Show in FAERS Data

> Show in Efficacy Data

Source

FDA approval package document: Approval Package (Page:4) View Full Study PDF 1016k

FDA approval package document: Approval Package (Page:12) View Full Study PDF 1270k

FDA approval package document: Approval Package (Page:12) View Full Study PDF 965k

FDA approval package document: Approval Package (Page:35) View Full Study PDF 3959k

FDA approval package document: Approval Package (Page:8) View Full Study PDF 5122k

Metabolizing Enz. & Transporters search results

3017 records from ME&T data: [Nilotinib Hydrochloride Monohydrate (537) OR Gadodiamide (0) OR Amikacin Sulfate (0) OR lopamidol (0) OR Famciclovir (73) OR Toremfene Citrate (103) OR Indacaterol Maleate (749) OR Bisoprolol Fumarate (78) OR Ipratropium Bromide (24) OR Ethinyl Estradiol (383) OR Drospirenone; Ethinyl Estradiol (0) OR Trandolapril (36) OR Tenofovir Disoproxil Fumarate (1034)]

Preclinical Data Clinical Data All Data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system	Species	Dose	Route
1	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	No activity (in vivo)	Unreported	Not applicable	Human	10 mg	O
2	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Substrate (in vivo)	Unreported	Not applicable	Human	Unreported	O
3	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Enzyme Substrate (in vivo)	CYP(unspecified)	Not applicable	Human	10 mg	O
4	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Transporter Inhibitor (in vivo)	MDR1	Not applicable	Human	10 mg/d for 4 days	O
5	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Substrate (in vivo)	Unreported	Not applicable	Human	Unreported	O
6	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Substrate (in vivo)	Unreported	Not applicable	Human	20 mg	O
7	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Enzyme Substrate (in vivo)	CYP(unspecified)	Not applicable	Human	10 mg	O
8	Bisoprolol Fumarate	Parent	Bisoprolol fumarate	Transporter Inhibitor (in vivo)	MDR1	Not applicable	Human	Unreported	O

再在结果集中，筛选酶抑制 'IC50'

Filters

Refine search:

Apply Clear all

Drugs

Routes of Administration

Sources

Data type

☒ Metabolizing Enzymes (2031)

☐ Drug as Enzyme Inducer (281)

☐ Drug as Enzyme Inhibitor (601)

☐ Enzyme Inhibitor (in vitro) (439)

☐ Activity (% inhibition) (47)

☐ Activity (no value) (66)

☐ I/Ki (5)

☐ IC25 (2)

☒ IC50 (158)

☐ IC50 (633)

➤ PP提供多种分类的选项交叉筛选：通过metabolizing...把代谢数据筛选出来

➤ 再在结果集中，筛选酶抑制 'IC50'

Pharmacokinetic---检索结果

- 通过快速的筛选，发现有两个上市的药物符合要求 (serum binding<1, CYP3A inhibition)
- 同时还有查看关于首过代谢抑制的细节，以及根据需要研究这两个药物的其他信息

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IP-authorized

29 records from ME&T data: [Nilotinib Hydrochloride Monohydrate (5) OR Gadodiamide (0) OR Amikacin Sulfate (0) OR Iopamidol (0) OR Famciclovir (0) OR Toremifene Citrate (0) OR Indacaterol Maleate (0) OR Bisoprolol Fumarate (0) OR Ipratropium Bromide (0) OR Ethinyl Estradiol (24) OR Drospirenone; Ethinyl Estradiol (0) OR Trandolapril (0) OR Tenofovir Disoproxil Fumarate (0)] AND [IC50 (29)] AND [CYP3A (29)]

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

Preclinical Data Clinical Data All Data

ID	Drug ▾	Metabolite ▾	Substance Studied ▾	Data Type ▾	Enzyme/Transporter ▾	Test system ▾	Species ▾	Dose ▾	Concomitant ▾
20	Ethinyl Estradiol		Ethinylestradiol	Enzyme Inhibitor (in vitro)	CYP3A4	Liver, microsomes	Human	0.01-45 uM	substrate
21	Ethinyl Estradiol		Ethinylestradiol	Enzyme Inhibitor (in vitro)	CYP3A5	Enzyme, recombinant	Human	Unreported	substrate
22	Ethinyl Estradiol		Ethinylestradiol	Enzyme Inhibitor (in vitro)	CYP3A4	Microsomes, recombinant	Human	Unreported	substrate
23	Ethinyl Estradiol		Ethinylestradiol	Enzyme Inhibitor (in vitro)	CYP3A(unspecified)	Liver, microsomes	Human	2.5-50 uM	substrate
24	Ethinyl Estradiol		Ethinylestradiol	Enzyme Inhibitor (in vitro)	CYP3A4	Microsomes, recombinant	Human	Unreported	In Vitro Fluorescein substrate
25	Nilotinib Hydrochloride Monohydrate		Nilotinib	Enzyme Inhibitor (in vitro)	CYP3A(unspecified)	Liver, microsomes	Human	1-100 umol/l	In Vitro 1'-hydroxymidazolam midazolam 5 uM
26	Nilotinib Hydrochloride Monohydrate		Nilotinib Hydrochloride Monohydrate	Enzyme Inhibitor (in vitro)	CYP3A4	Liver, microsomes	Human	Unreported	In Vitro Ketoconazole ketoconazole
27	Nilotinib Hydrochloride Monohydrate		Nilotinib Hydrochloride Monohydrate	Enzyme Inhibitor (in vitro)	CYP3A4/5	Liver, microsomes	Human	Unreported	In Vitro Testosterone testosterone

Show Filters ▾

Show drugs in

Deselect all
Export All drugs in Excel file (.xls)
Show the filtered drugs in other modules. Based on your filtering.

Selected: 2

☒ Ethinyl Estradiol
☒ Nilotinib Hydrochloride Monohydrate

> Show in Pharmacokinetic Data
> Show in Drug Safety Data
> Show in FAERS Data
> Show in Efficacy Data
> Show in Activity Data

Pharmacokinetic---原文查看

FDA Approval Package - Nilotinib Hydrochloride Monohydrate > Pharmacology Review

Pharmacology Review 022068/S-000 Part 01

1/25 Go

no additional non-clinical studies are necessary for approval for the proposed indication.

C. Recommendations on labeling
A separate review will be conducted.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Nilotinib (AMN107) is a kinase inhibitor that targets Bcr-Abl, c-Kit and platelet derived growth factor (PDGF) receptor, via an ATP-competitive mechanism.

Orally administered nilotinib was absorbed rapidly (T_{max} 0.5-4 hr), with bioavailability ranging from 20 to 43% in the tested rodent (mice and rats) and non-rodent (rabbits and monkeys) species. The plasma protein binding of nilotinib was high (over 97% in all tested species), and bile, uveal tract (pigment layer in the eye), stomach glandular, liver, and adrenal gland, had highest nilotinib concentration. Although nilotinib showed little penetration through the blood-brain and blood-testis barrier, it crossed the placenta and entered the fetuses. Nilotinib was found in the milk of lactating rats after a single oral dose. The biotransformation of nilotinib was primarily oxidation, oxidative cleavage of the imidazole ring, amide bond hydrolysis, and glucuronic acid conjugation. The commonly found metabolites in rat, dog, monkey and human were P20, P36, P36.5, P41.6, P42.1, P47 and P50. The rat and monkey profiles were most similar to that of human, and that in dog was the least. One of the major metabolites in human, P36.5 (approximately 7% AUC of parent drug), was also found in plasma of monkey but not other species. Cytochrome P450 (CYP) 3A4 was responsible for the hepatic oxidative clearance of nilotinib. In *in vitro* studies, nilotinib inhibited CYP 2D6, 2C19, 2C9, 3A4, 2C8, UGT1A1 and P-glycoprotein, but induced CYP 2B6, 2C8, 2C9, 3A4, 1A1, 1A2 and UGT1A1. The main excretion after oral doses was fecal. After repeated administration (4 to 39 weeks), while the accumulation was not seen in every dose group in rats, nilotinib accumulated in dogs (in both sexes at higher doses) and monkeys (in both sexes at all doses tested). The systemic exposure to nilotinib increased with dose, and was generally proportional in rats, but less than proportional in dogs and monkeys.

The safety pharmacology studies in rat, rabbit and dog, and general toxicology studies in rat, dog and monkey identified liver, bile duct, gall bladder, lung, spleen, heart and pancreas as the target organs. The major findings are as the follows:

1

This document shows original U.S. government data provided by the U.S. Food & Drug Administration and is available in the public domain. It has been processed to facilitate searching and data extraction and may be viewed at www.pharmapendium.com

8 of 85

➤ 对于首过代谢实验细节的描述，有助于在研药物参考，选择动物模型，测试方向等等

对DDI risk 的评估贯穿整个药物研发的全流程

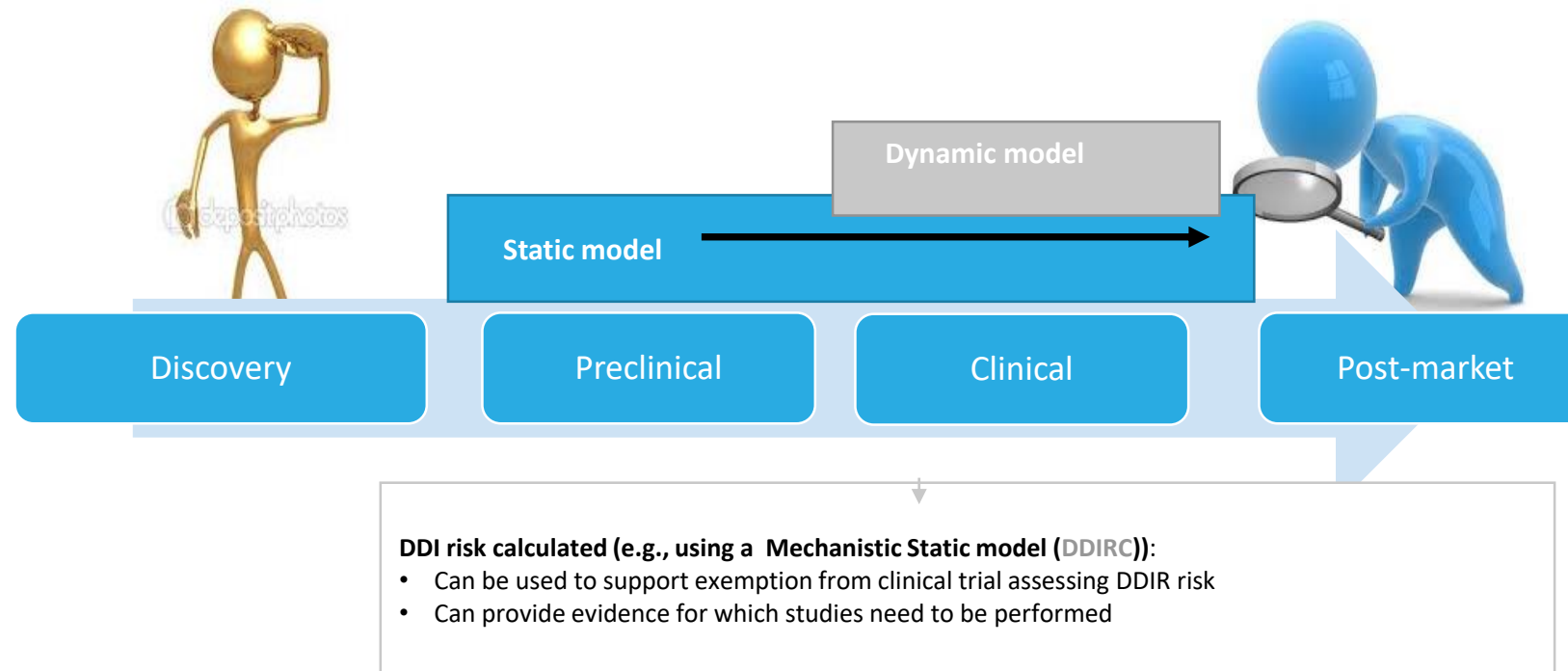
—FDA推荐逐步渐进的，基于新陈代谢相互作用的模型的评估方式
The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

Early development: a wider look

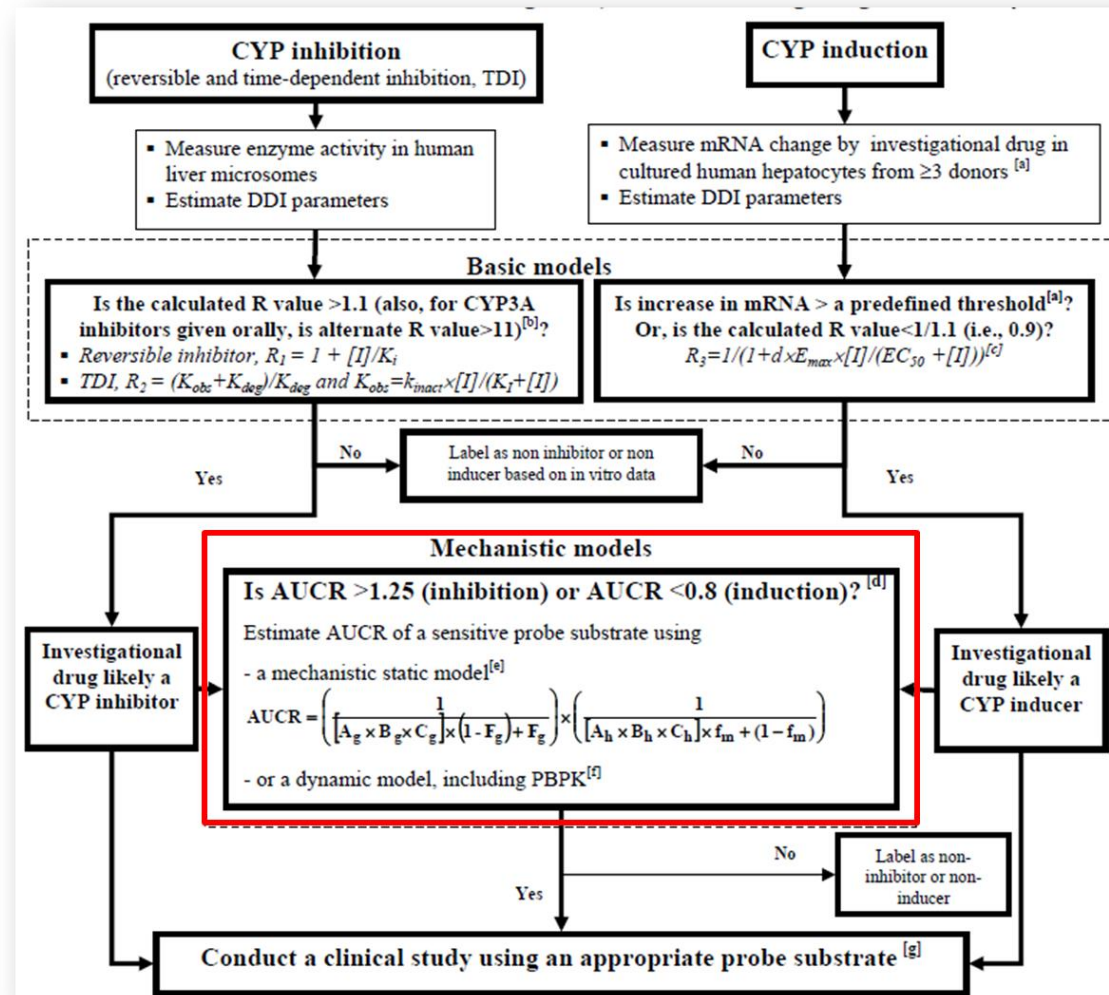
- **Mechanistic Static models** (e.g., **DDI Risk Calculator**) provide an overview of all potential DDIs
- Default parameters in DDIRC allow early predictions. These values are updated with experimental data later on for precise predictions

Later in development: a closer look

- Information in **Dynamic and Static** models is **complimentary** and used to assesses DDI Risk between specific drugs and to determine what drugs can be used along with a candidate in clinical studies
- Mechanistic Dynamic Modelling (PBPK modelling) requires significant input data and the availability of a PBPK model for each interacting drug



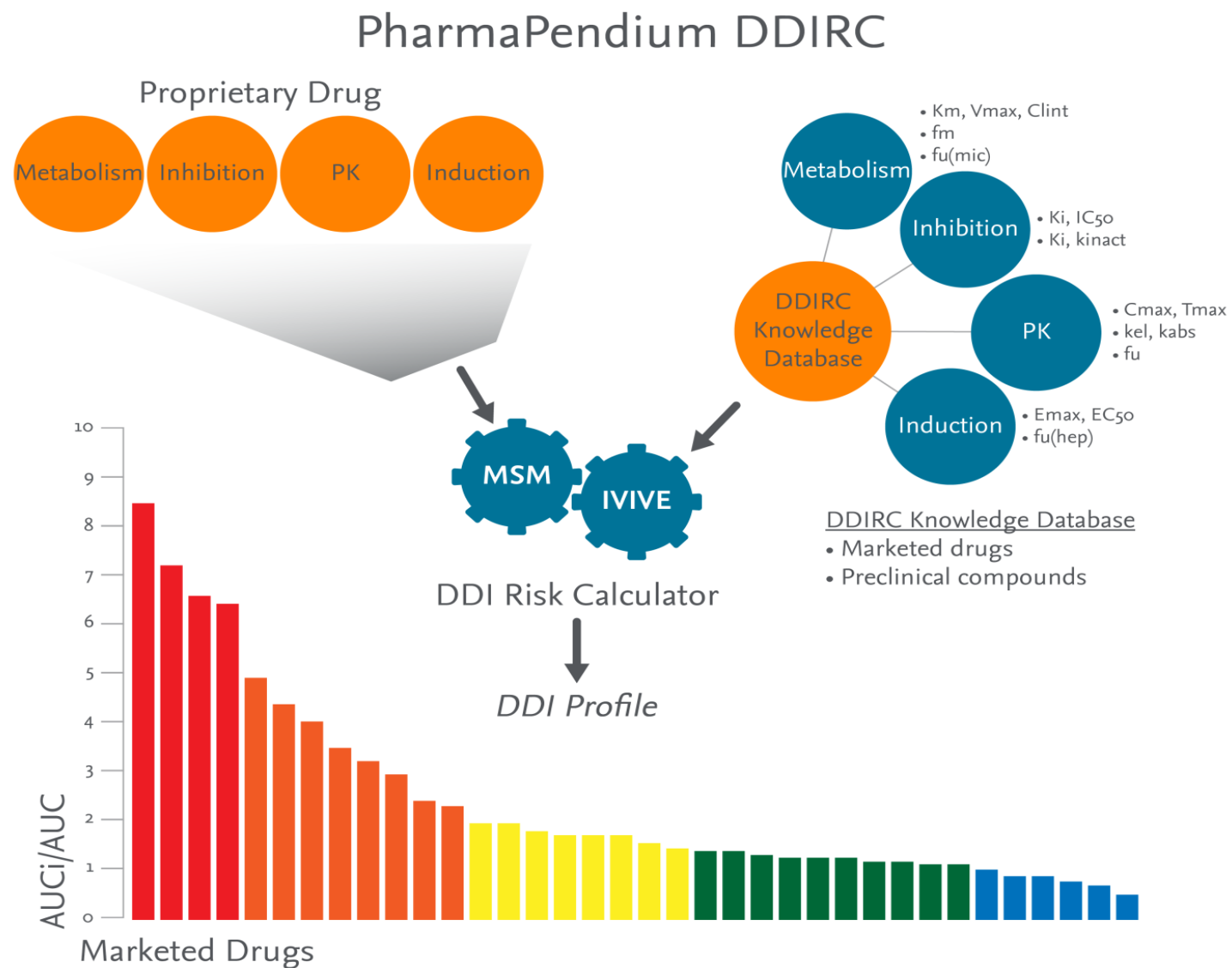
PharmaPendium's Drug-Drug Interaction Risk Calculator (DDIRC) 是遵循 2012 and 2017 FDA guidance



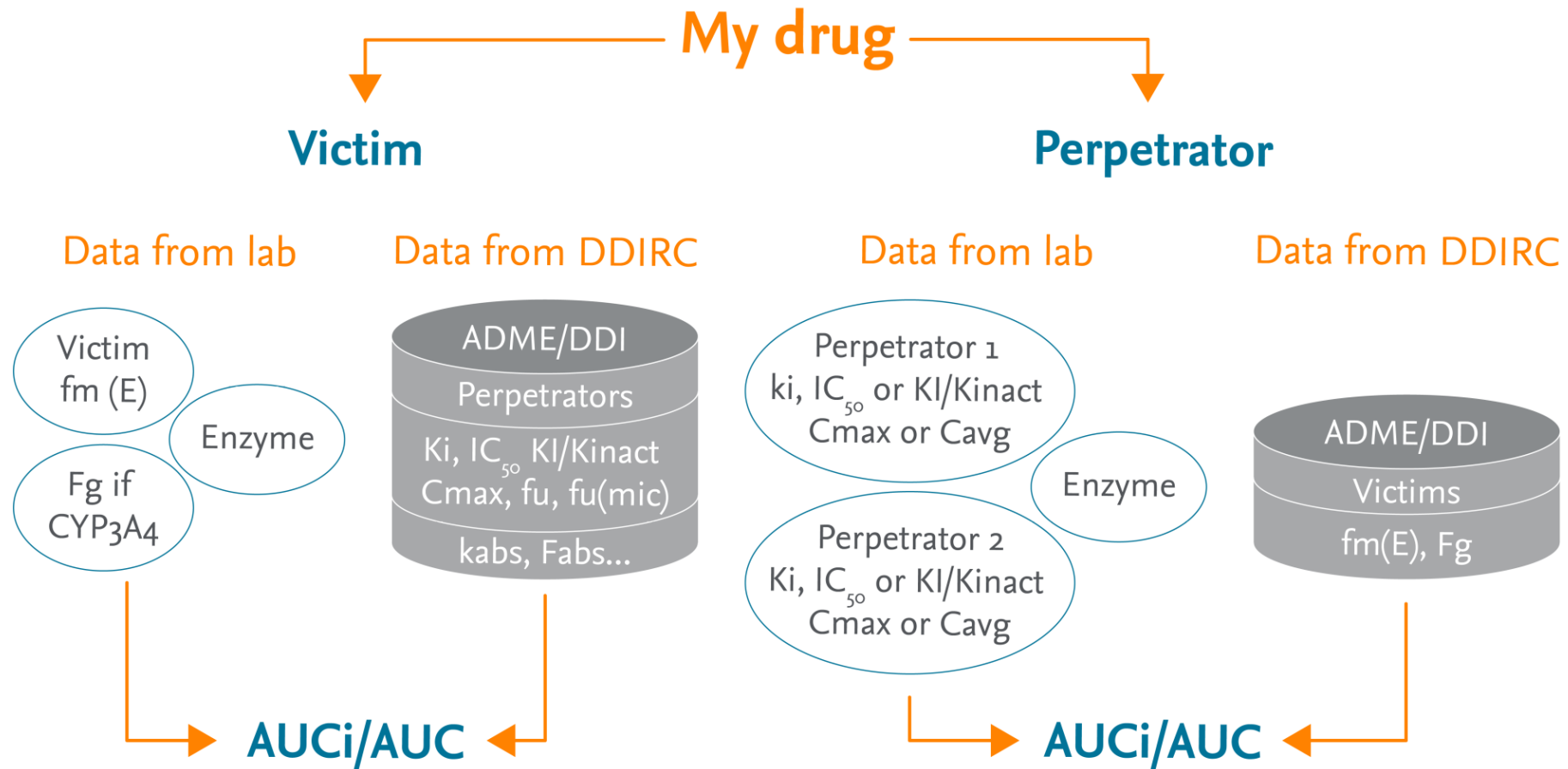
Guidance for Industry Drug Interaction Studies
Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations

“This guidance reflects the Agency’s view that the pharmacokinetic interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug’s safety and effectiveness”

DDI RC an IVIVE 基于的是静态的方法

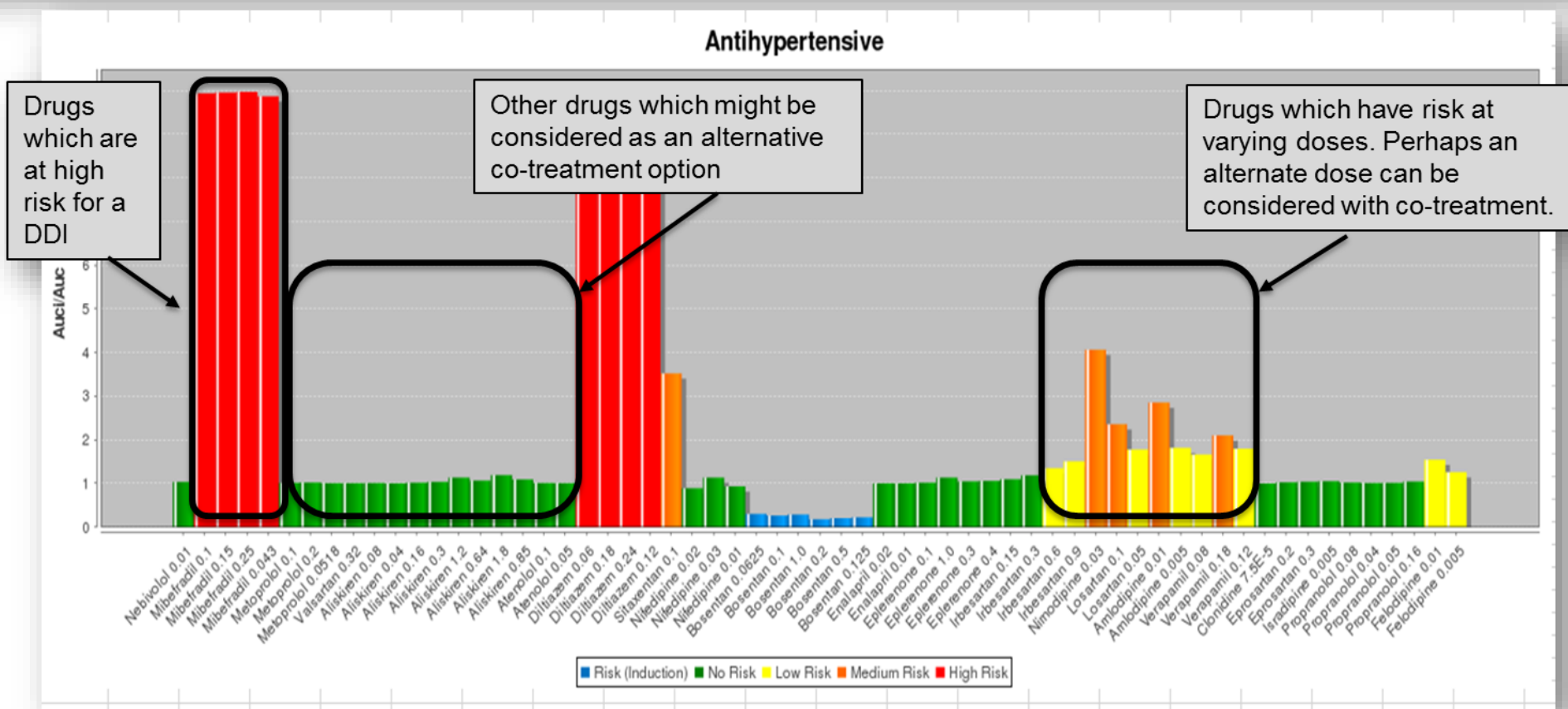


DDIRC 可以自动的运行和操作帮助我们节约了大量的时间



DDIRC 可以快速的提供成百个药物的潜在的相互作用

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?



Pharmpendium's DDIRC

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All These Sources ▾

e.g. Coronar* artery disorders

Search >

☐ Include synonyms

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



Pharmacokinetic Data



Metabolizing Enz. & Trans. Data



Drug Safety Data



FAERS Data new



Chemistry Search



Efficacy Data



Activity Data



DDI risk calculator

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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

Pharmpendium's DDIRC

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Proprietary Victim

Victim Perpetrators

Please enter proprietary data for the v

Victim definition

*Compound name:

Hepatic Metabolism

☒ User Defined
☐ Predicted

Enzyme(s)

CYP1A1 ▾

CYP2B6 ▾

Select ▾

Predict interactions

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DDI Prediction

91 records from DDI Risk Calculator: victim: gefitinib

Filters ▾

Refine search:

Apply

Clear all

Therapeutic Classes ▾

Molecules ▾

Drug Type ▾

Results

ID

Perpetrator ▾

⌕ ↑

Doc

MBL

AUC Ratio

Count

Min

Max

Hide Filters ▾

1

(-)-Omeprazole
162827

Antilcerative
Proton pump inhibitor

Dev.: -
Drug Type: Approved

Mul

2

Alvimopan
136195

Laxative

Dev.: +
Drug Type: Approved

Mul

...

3

Amitriptyline
4815

Analgesic: non narcotic
Antidepressant

Drug Type: Approved

0.02

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/GuidanceComplianceRegulatoryInfor...>

感谢聆听，欢迎交流，以及批评指导

THANK YOU!

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18516129056 张弦

