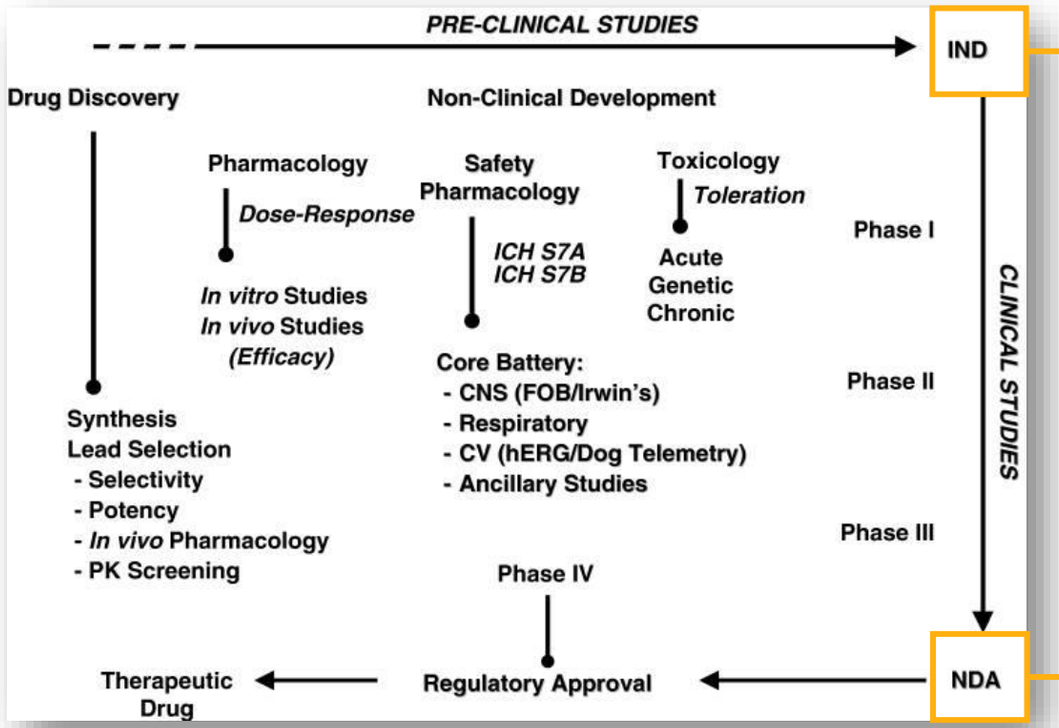
如何利用Pharmapendium数据库支持药物研发

张弦 吴鹏 Elsevier 生命科学 解决方案经理

目录

CONTENTS

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**

Reaxys

Reaxys Medicinal Chemistry

Pharmapendium

Embase

定量数据（数值，图谱，反应方程式

定性数据（结论，解释，过程描述等）

辅助决策

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

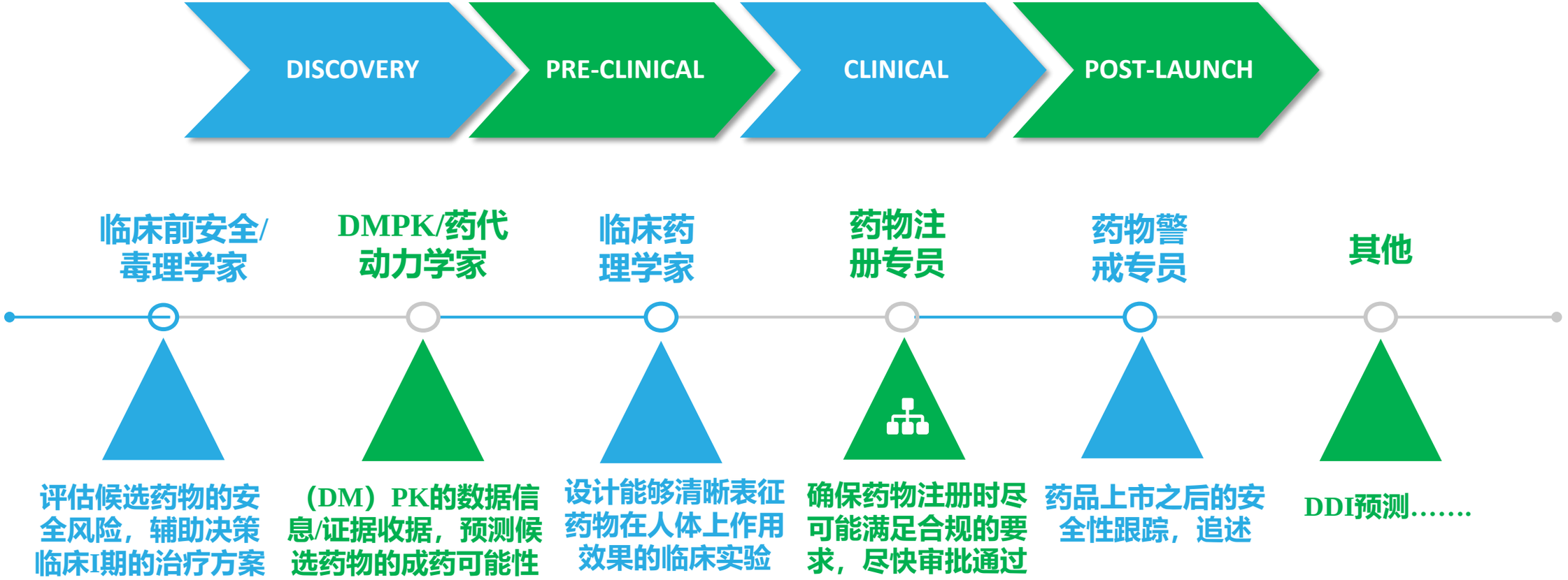
检索上市药物动物模型设计方案与数据

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

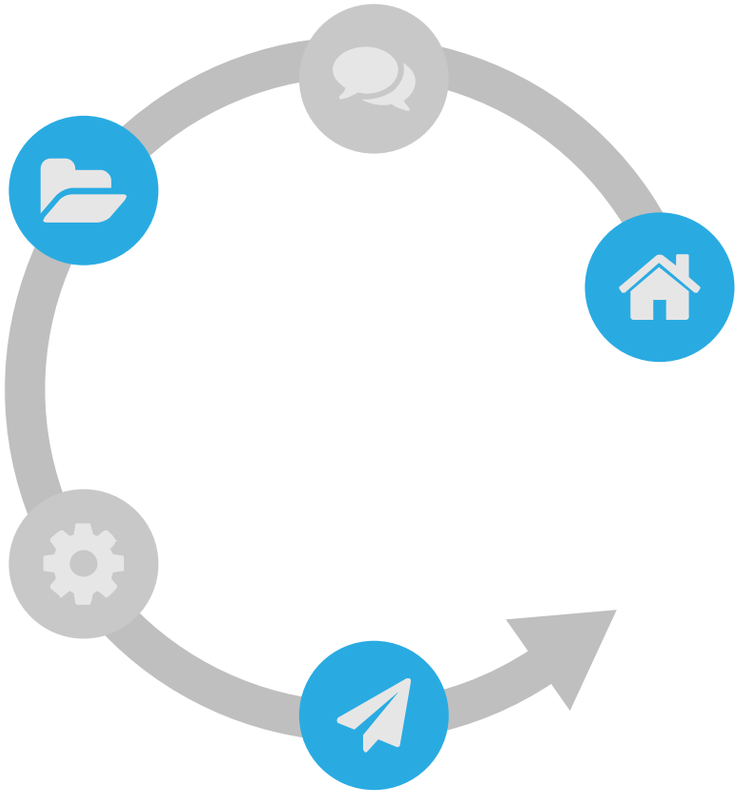
FDA & EMA所有的approval package（FDA: 1938年- 今， EMA: 1995年— 今）

2.29M+	200K+	9.45M+	673K+
pages of FDA approval documents	pages of EMA approval documents	FDA AERS reports	Pages from FDA Advisory Committee Meetings

Extracted Data

4450	1.6M+	305K+	1.66M+	2.45M+	115K+
Drugs indexed & fully searchable	PK data lines	Metabolizing enzyme and transporter data lines	safety data lines	efficacy data lines	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

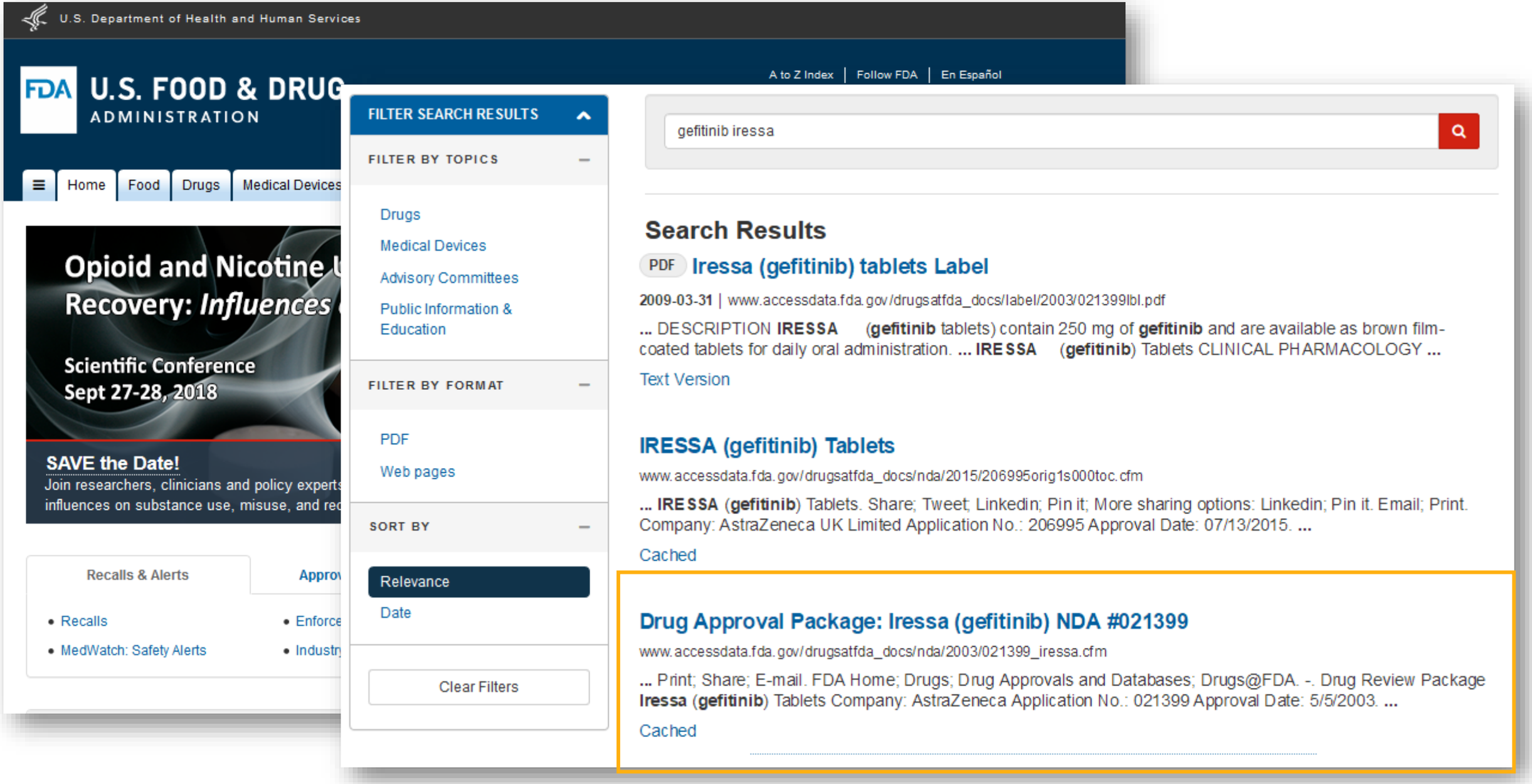
PharmaPendium与 Drugs@FDA比较

	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



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	1^0 endpoint	2^0 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

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®

Browse Search My tools new xian zhang

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

FDA Approval Package - Gefitinib > Medical/Clinical Review

Medical/Clinical Review 021399/S-000 Part 01

115% clinical review 26/198 Go

CLINICAL REVIEW

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Refractory	Stage III/IV PS 0-2 LCS ≤20	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06

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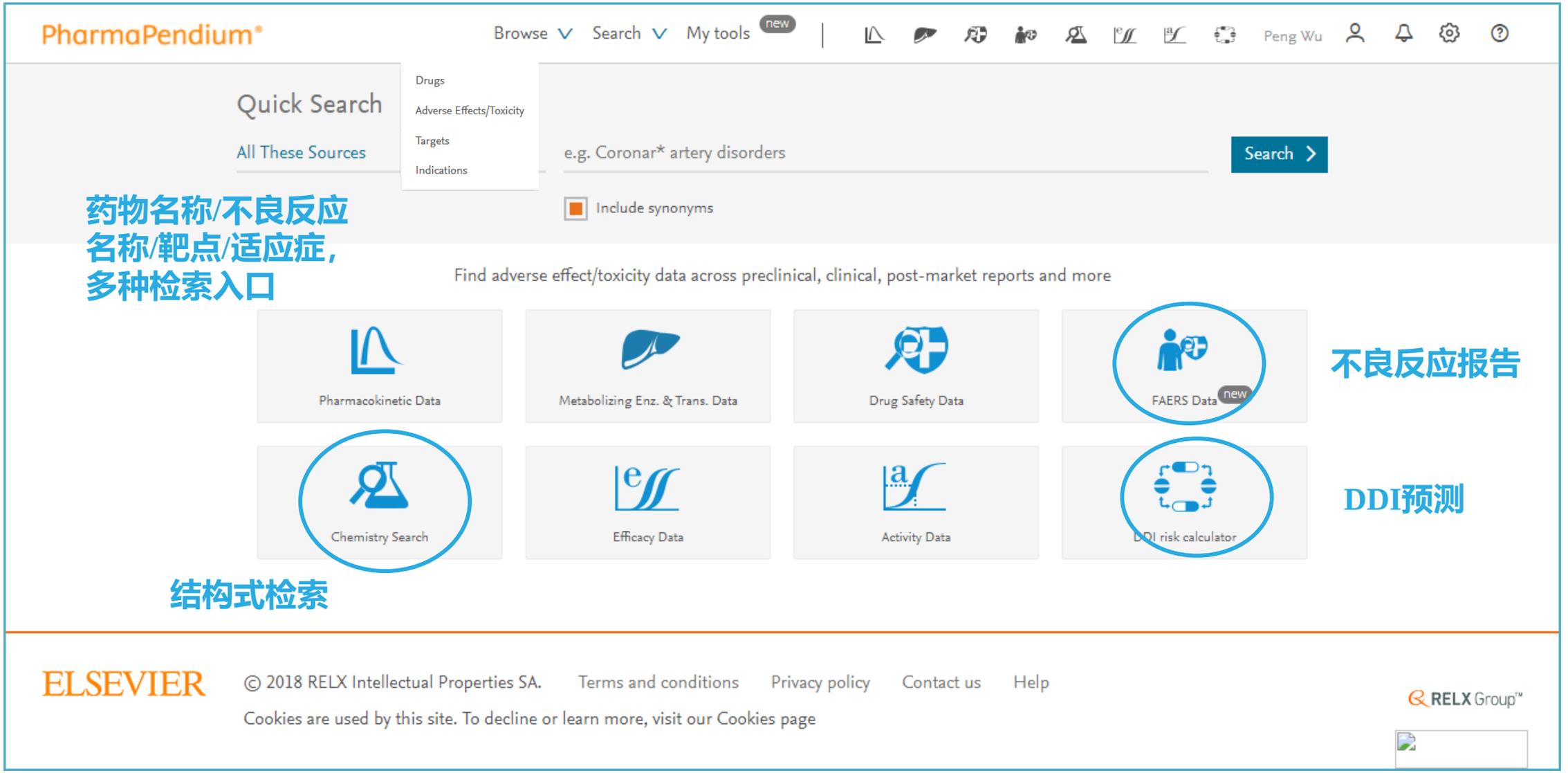
Pharmapendium检索界面直观清晰—支持结构，靶点，适应症检索



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**

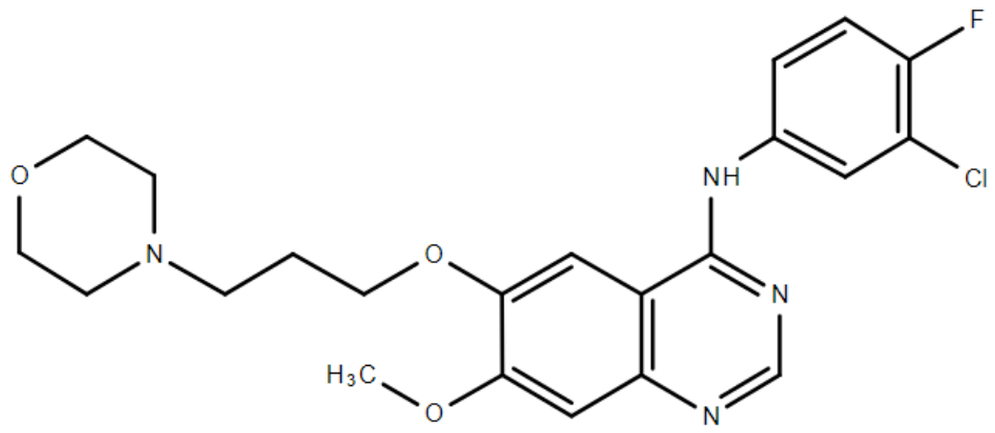
PharmaPendium® Browse Search My tools new

Chemistry search

Search criteria

Chemistry Structure

substructure search



Browse drugs - Antineoplastics > Antineoplastics, signal transduction inhibitors

Gefitinib

Brands: Geftinat; 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*:

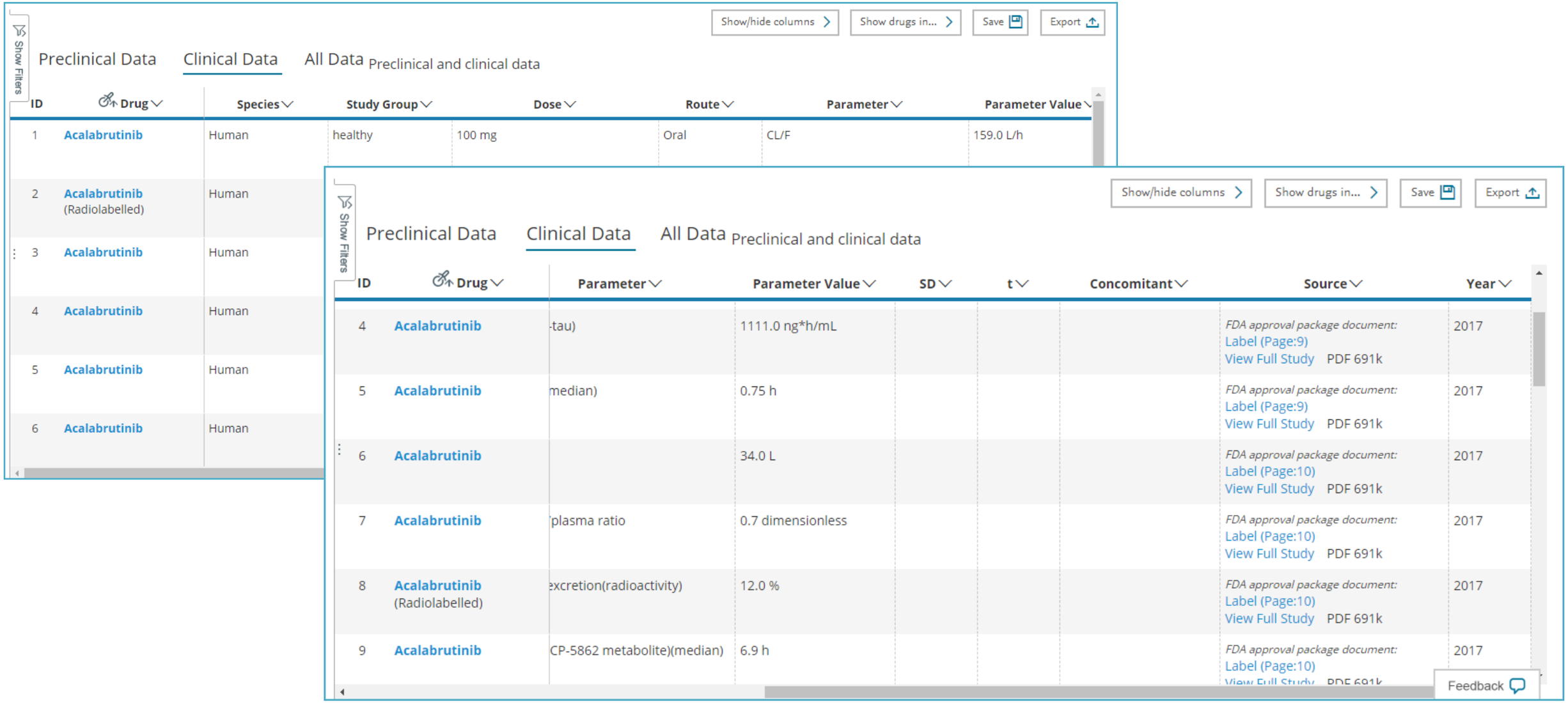
Viewing by area affected View by name

	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**



PharmaPendium-数据的优势

- **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.

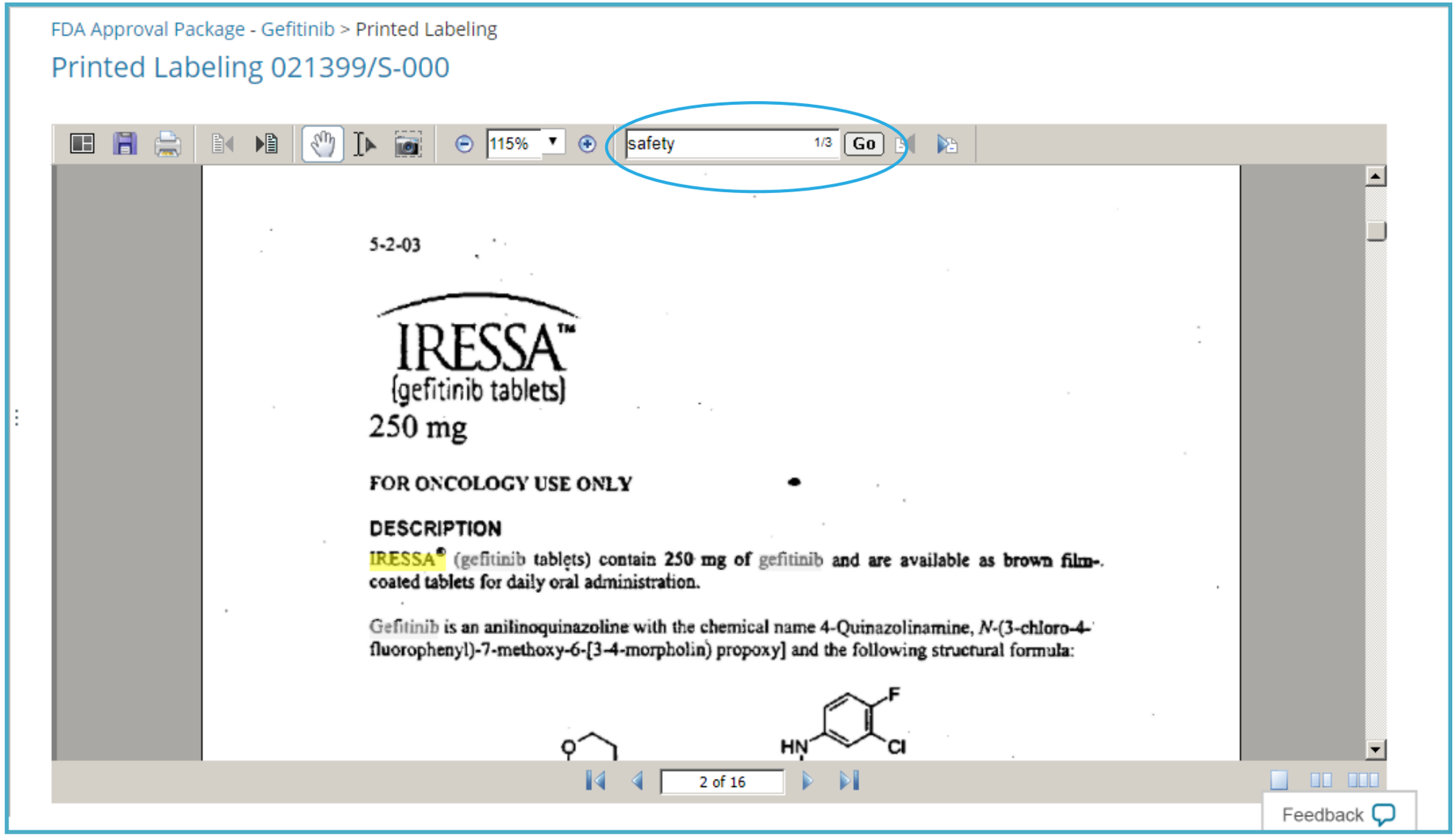
TABLE 1 Demographic and Disease Characteristics

	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**



对比FDA官网信息检索

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

- ABILIFY (ARIPIPRAZOLE) | NDA #021729 | TABLET, ORALLY DISINTEGRATING;ORAL | Discontinued | OTSUKA
- ABILIFY (ARIPIPRAZOLE) | NDA #021866 | INJECTABLE;INTRAMUSCULAR | Discontinued | OTSUKA

ABILIFY MAINTENA KIT

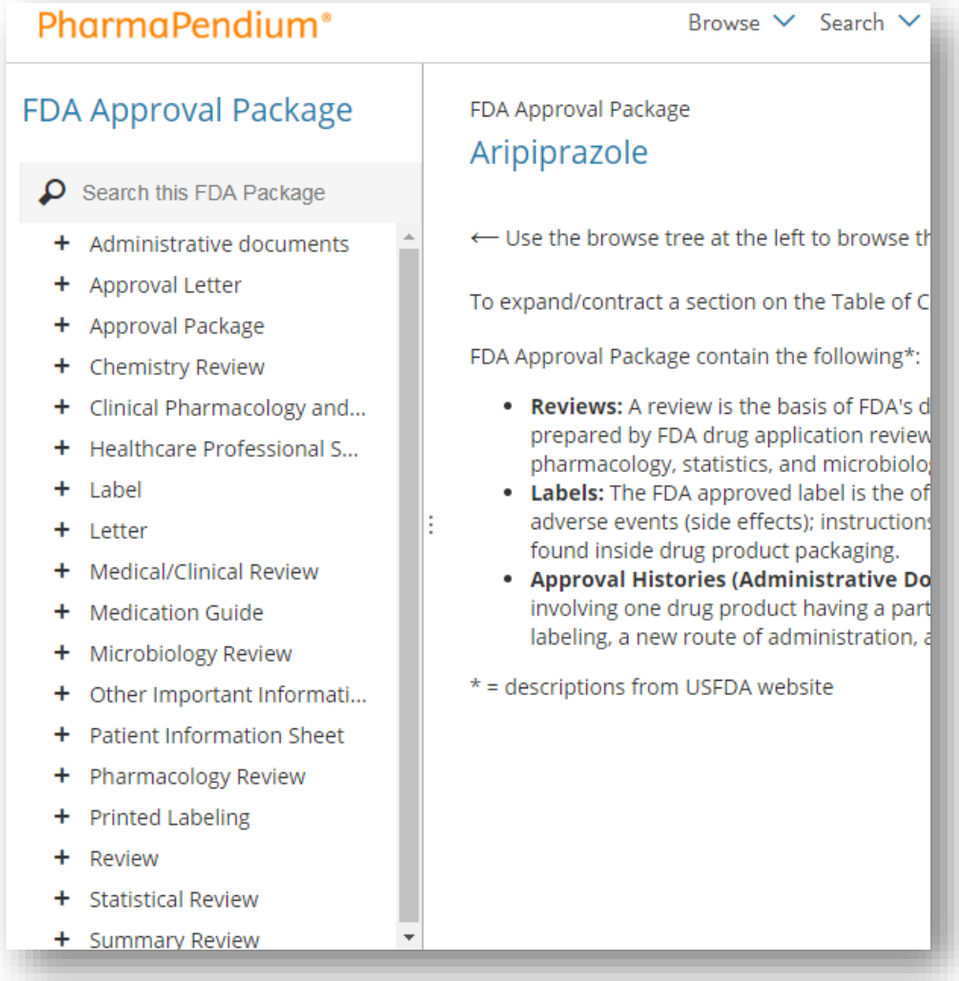
ABILIFY MYCITE KIT

ARIPIPRAZOLE

- 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



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

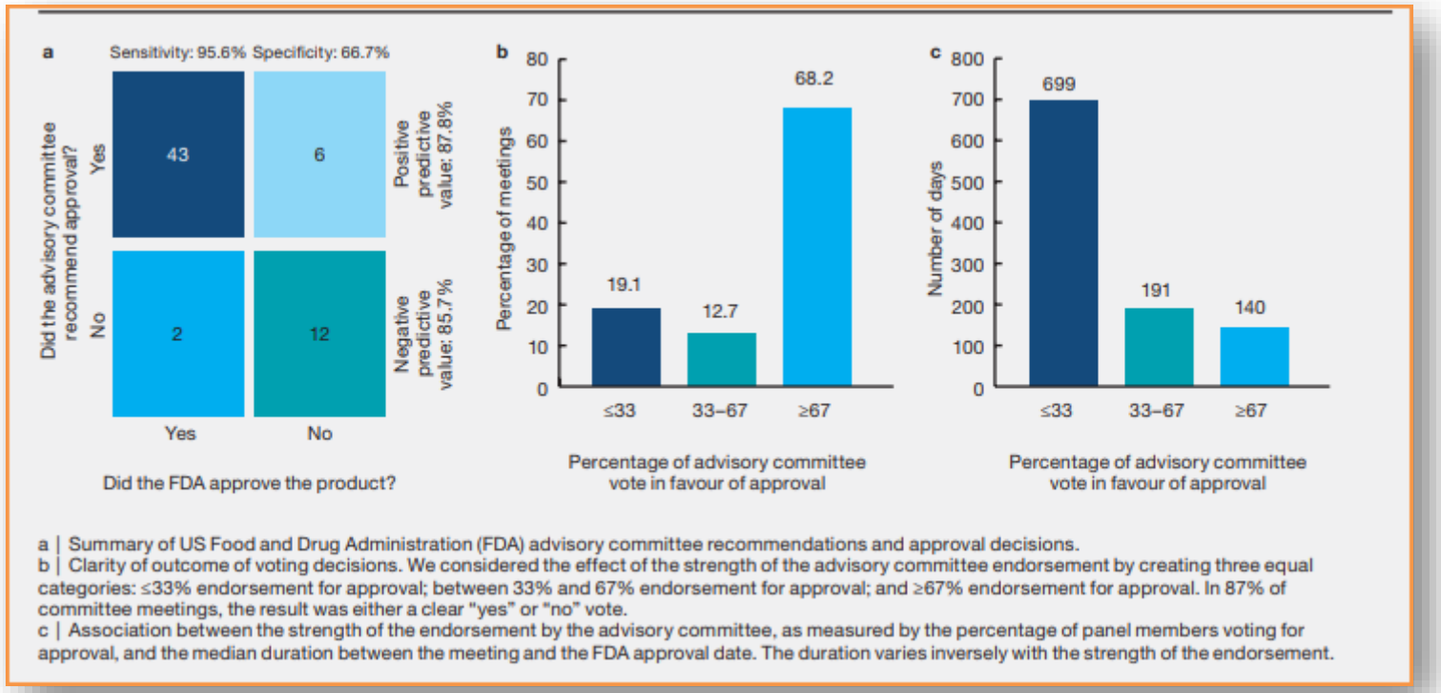
FDA Advisory Committee-AC报告的检索

Empowering Knowledge

FDA Advisory Committee Meeting reports-FDA AC 报告

- 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

2001-2010 FDA新药上市申请为例

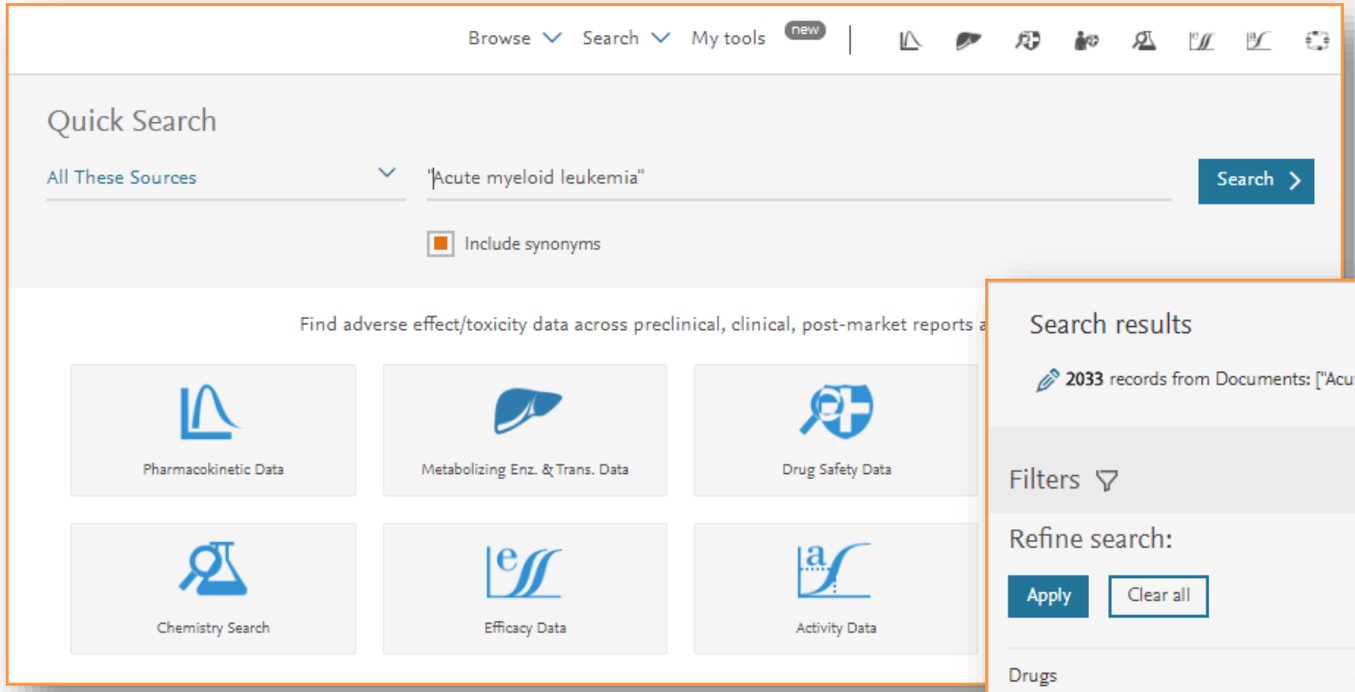


a | Summary of US Food and Drug Administration (FDA) advisory committee recommendations and approval decisions.
b | Clarity of outcome of voting decisions. We considered the effect of the strength of the advisory committee endorsement by creating three equal categories: ≤33% endorsement for approval; between 33% and 67% endorsement for approval; and ≥67% endorsement for approval. In 87% of committee meetings, the result was either a clear "yes" or "no" vote.
c | Association between the strength of the endorsement by the advisory committee, as measured by the percentage of panel members voting for approval, and the median duration between the meeting and the FDA approval date. The duration varies inversely with the strength of the endorsement.

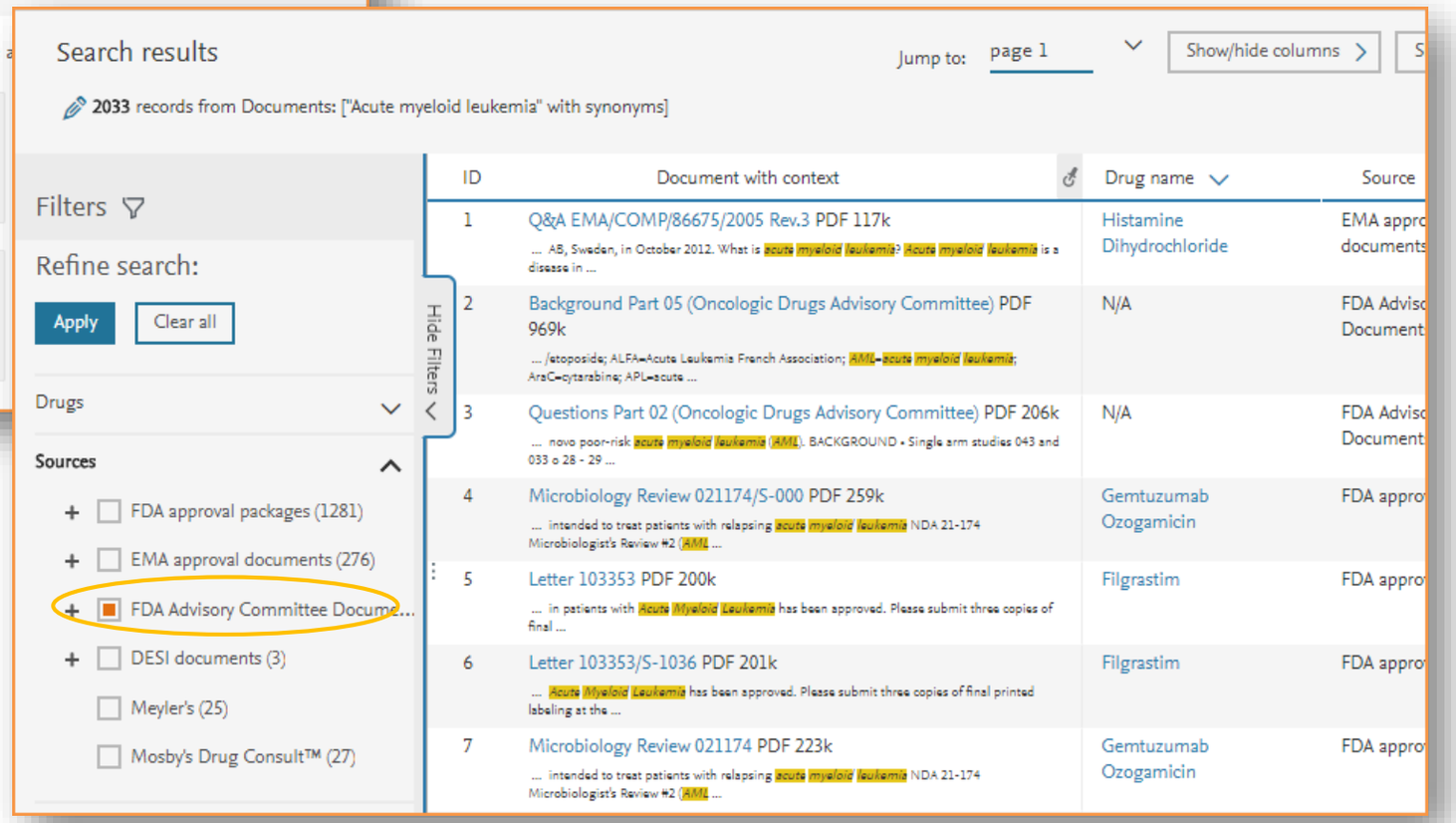
https://www.mckinsey.com/~/media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx

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



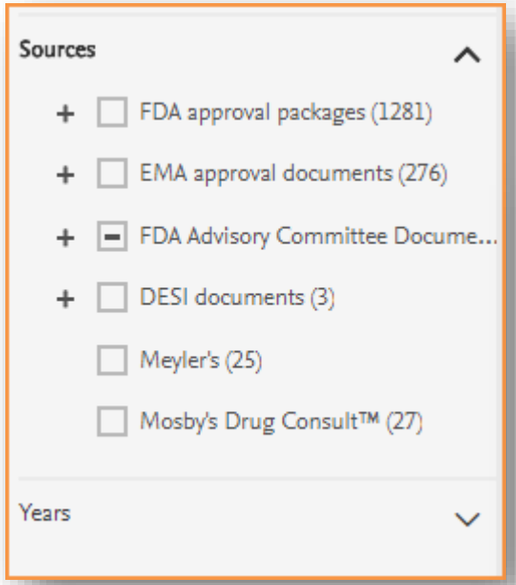
1. 直接输入 ‘“Acute myeloid leukemia”’ 进行free text检索

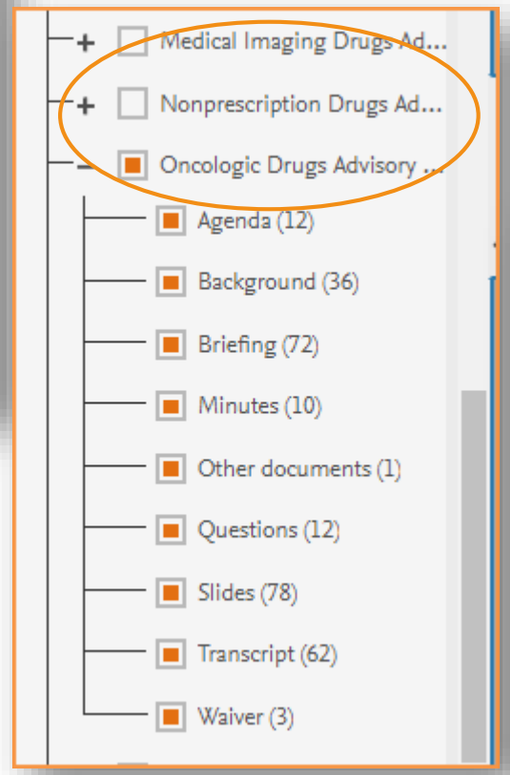


2. 结果集中，通过 ‘sources’ 的筛选可以直接找到AC报告

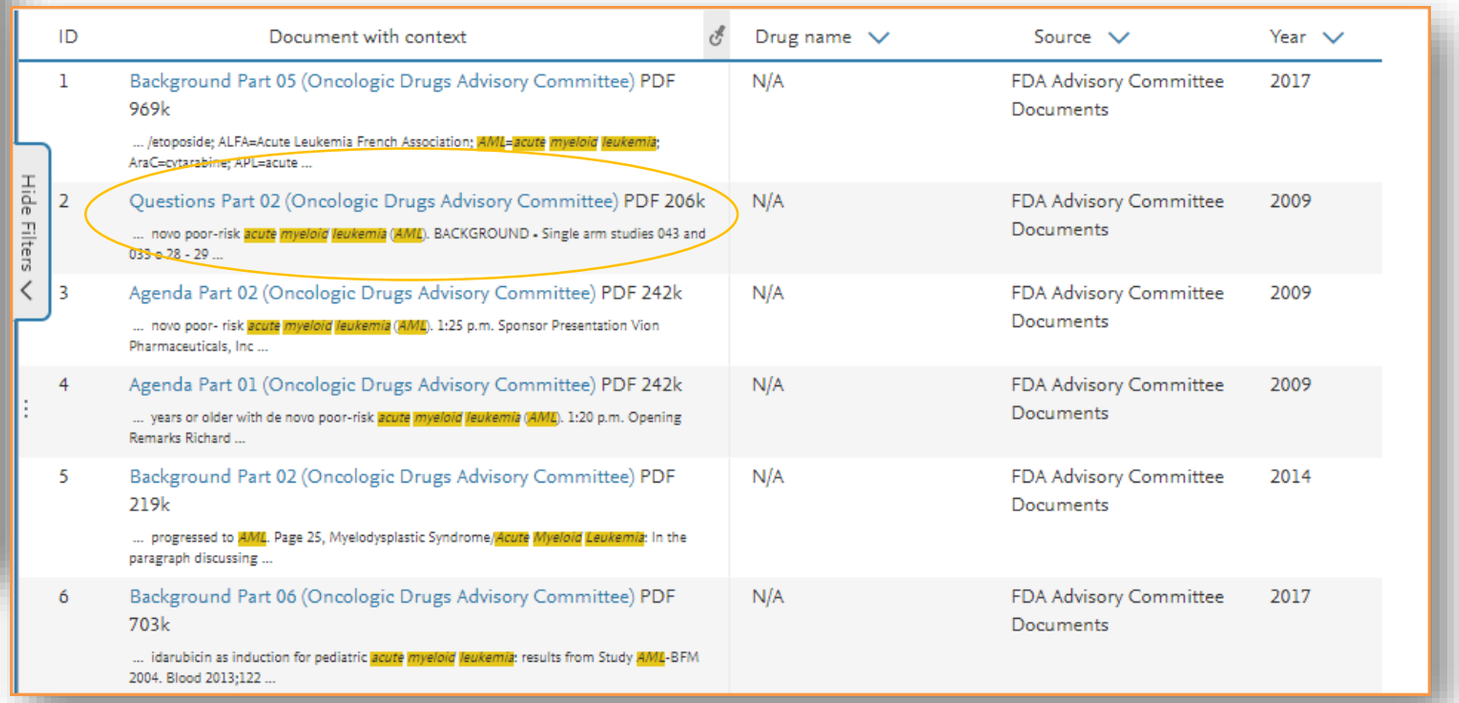
FDA-AERs---上市后副作用监控

- 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



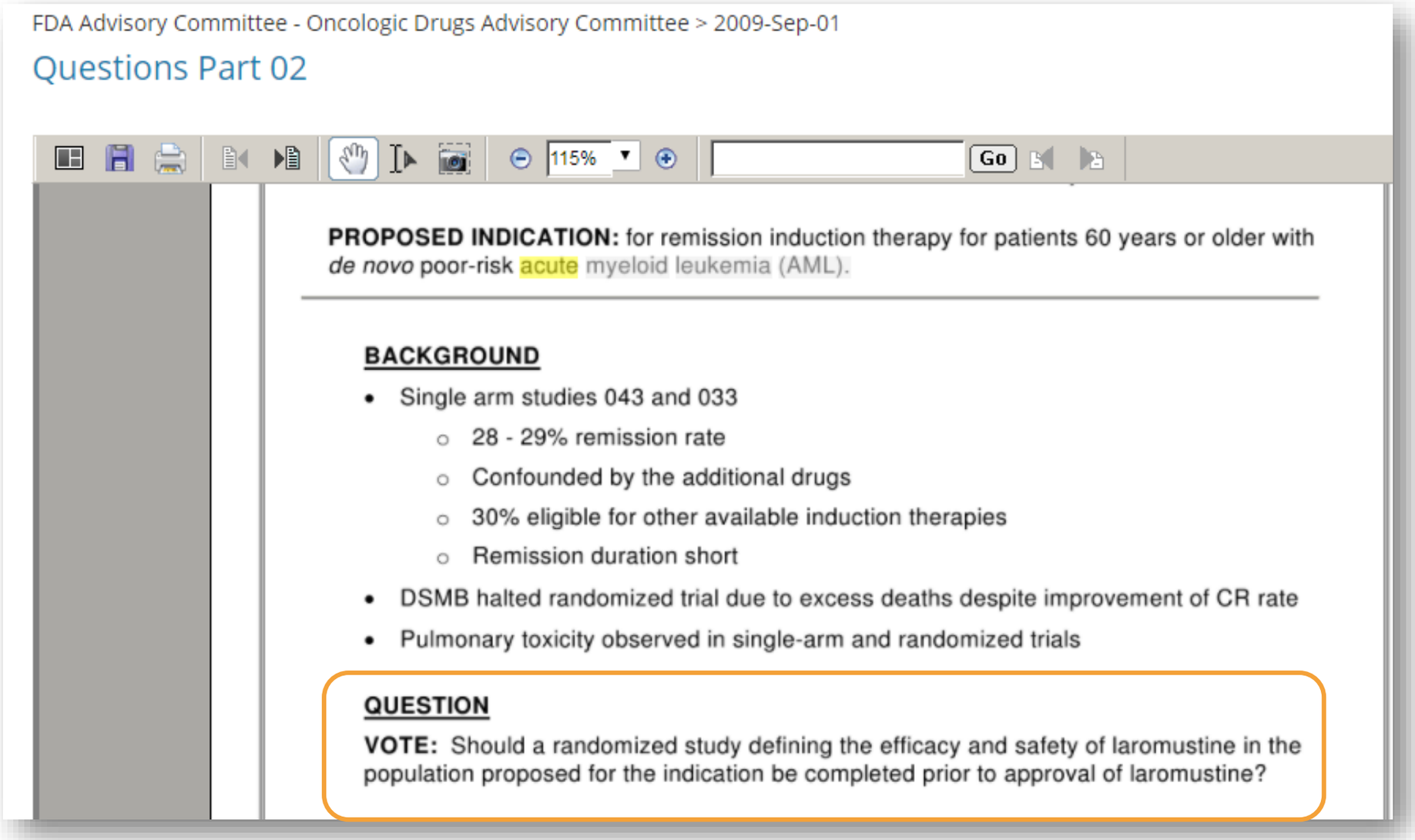


- 通过筛选器，快速便捷的得到了，关于治疗AML的肿瘤药物的AC报告结果集点击即可查看原文结果



- 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.....

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?

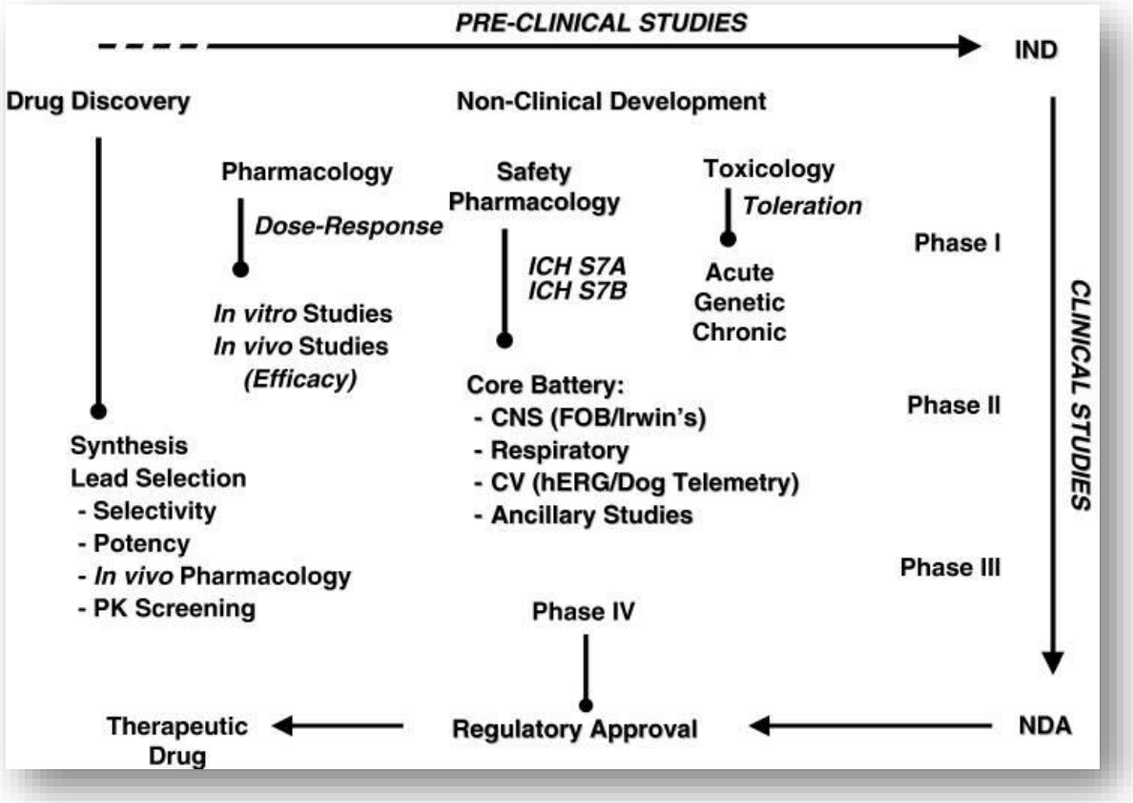
- 随机对照组实验,能够验证laromustine在前期递交申请中提到的对目标人群适应症的治疗药效和安全性吗?

临床前毒理----QT延长趋势研究

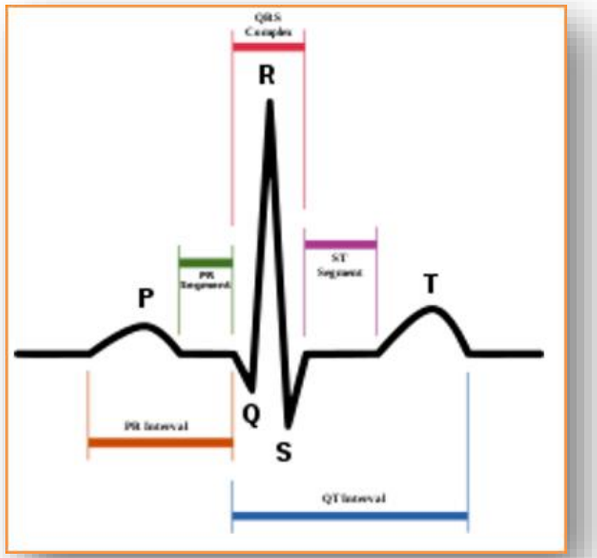
Empowering Knowledge

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



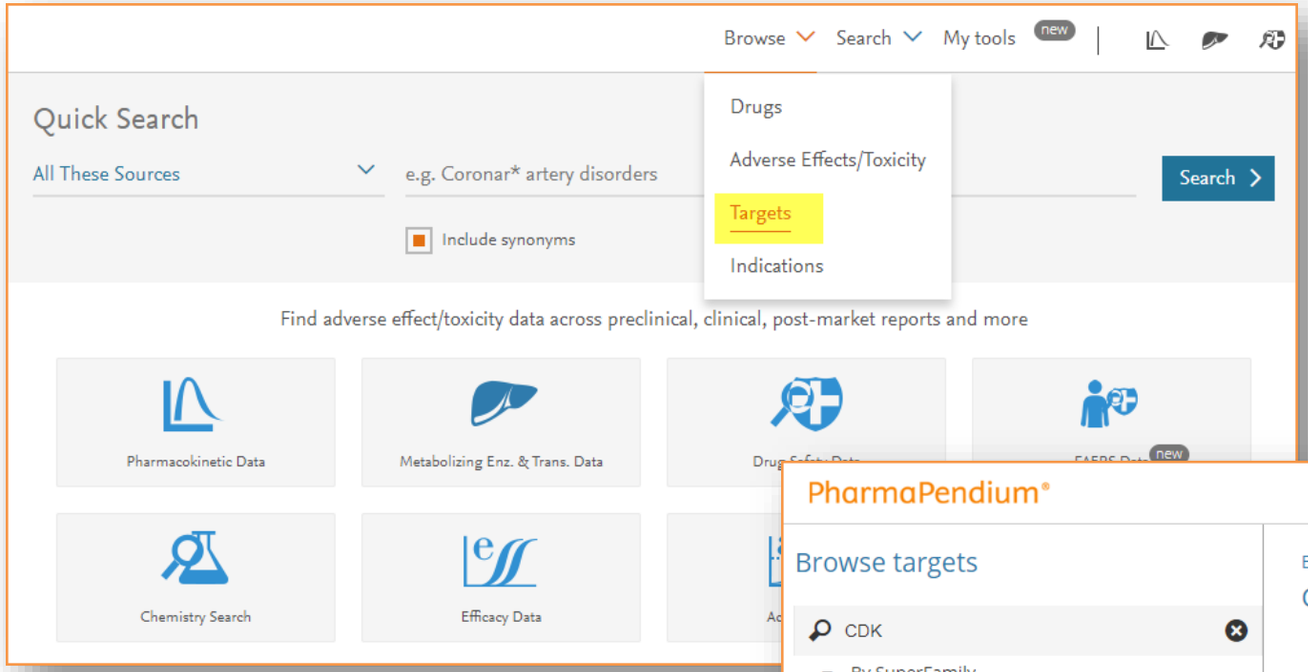
QT interval （QT间隔） 在心脏心电周期中Q信号和T信号的间隔周期是非常重要的检测指标. 它们的时长指标能够指示快速心率失常的潜在风险



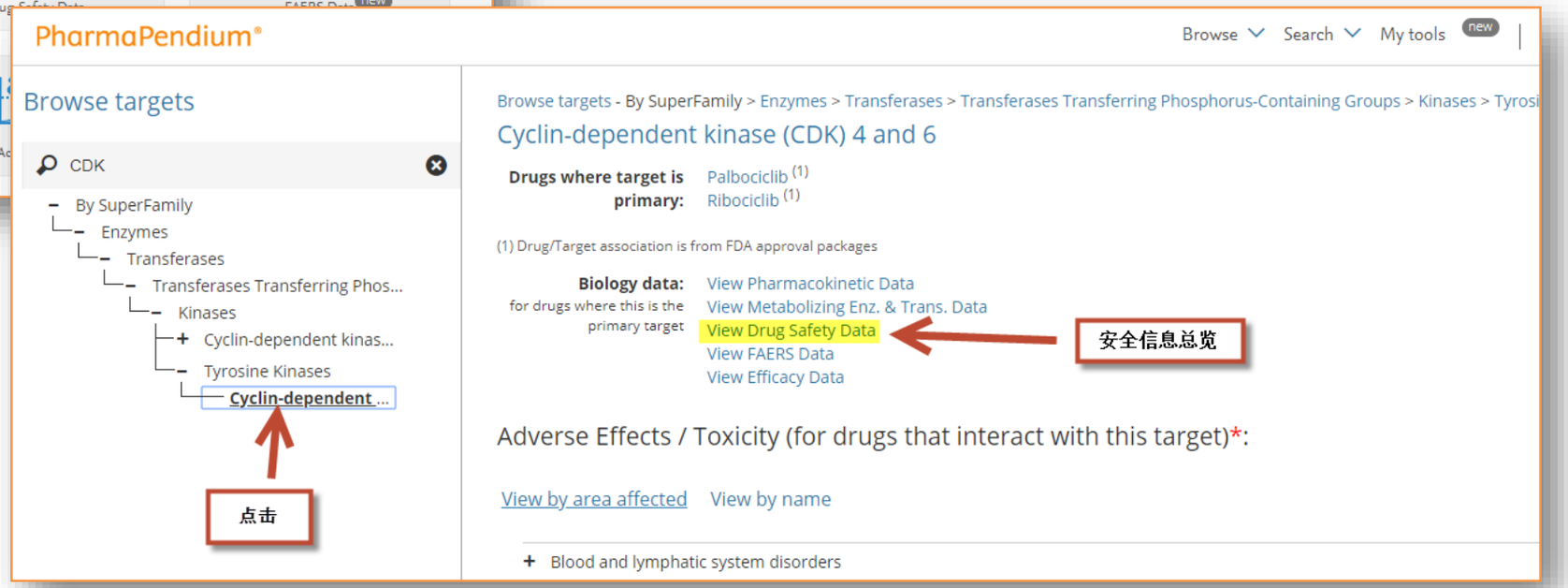
2005年以后，FDA和EMA要求几乎所有的的新药都要进行彻底的QT研究，验证新药分子对于QT interval（间隔）的影响.

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）

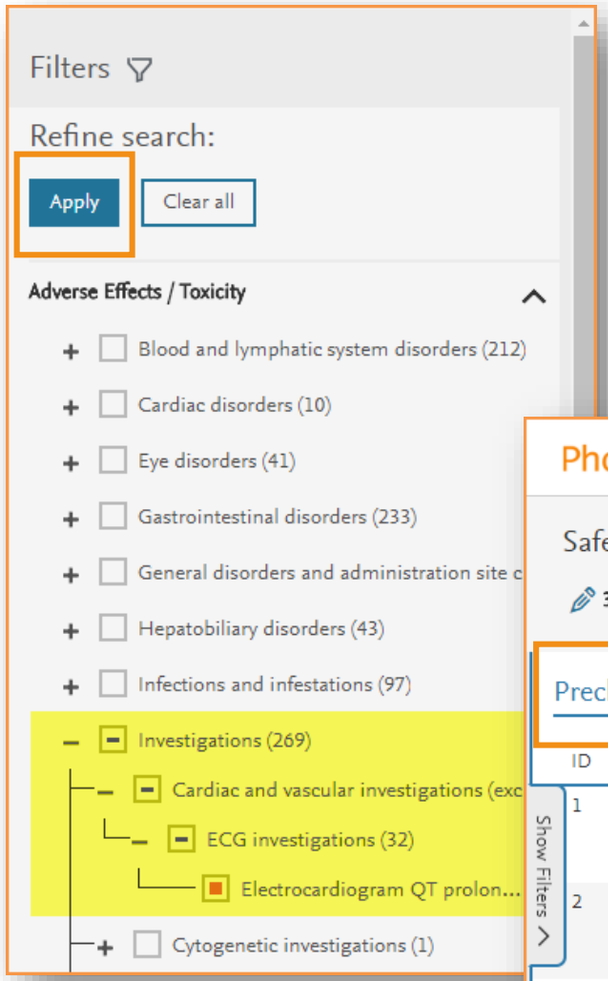


1. 在检索主界面选择靶点 ‘target’ 检索
2. 在新界面输入 ‘CDK’ 并找到改靶点的总览信息



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

PharmaPendium®

Browse Search My tools new

Safety data search results

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

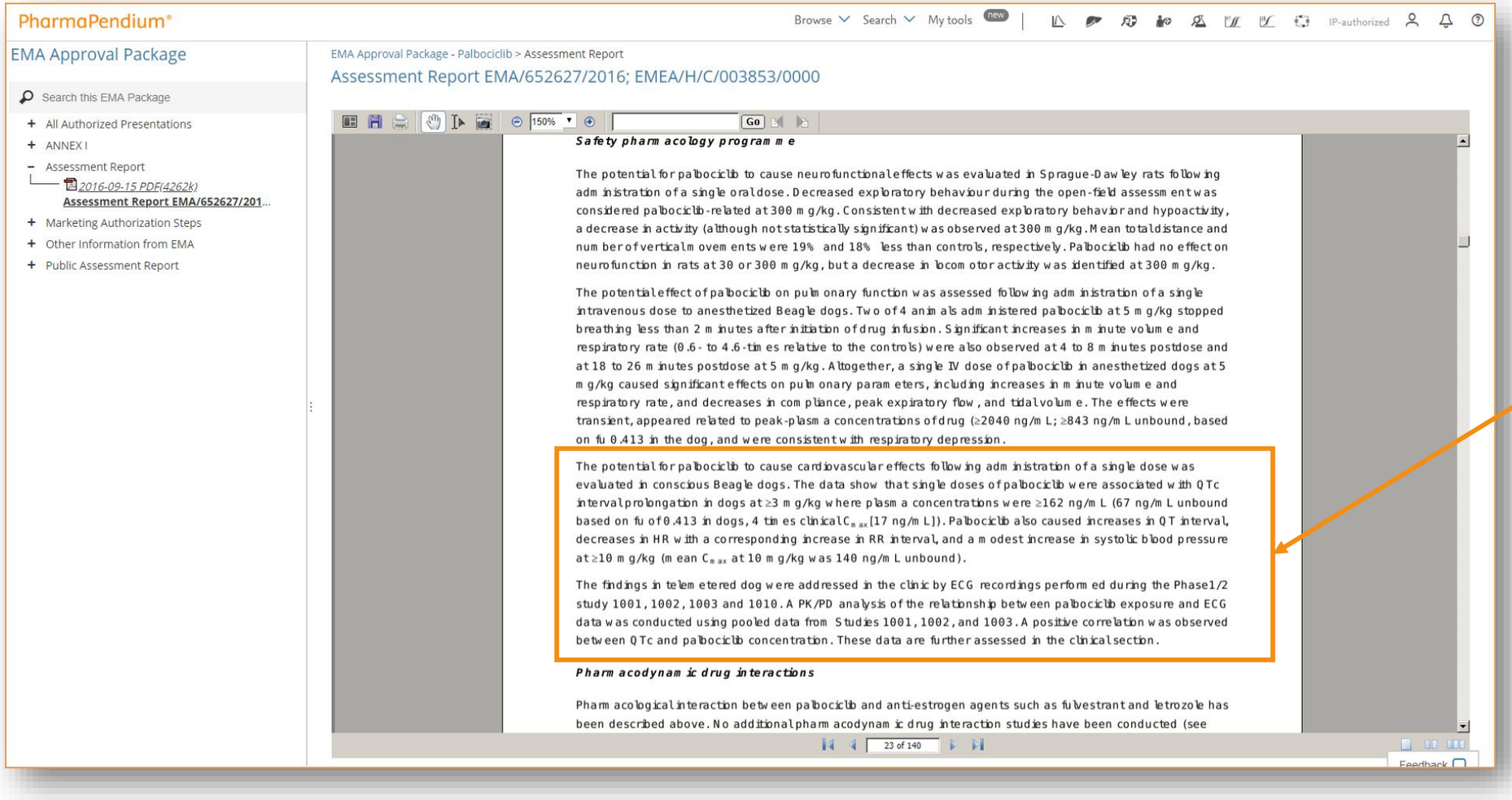
Preclinical Data | Clinical Data | Post-Marketing Reports (AERS) | All Data

Show Filters

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
1	Palbociclib	Electrocardiogram QT prolonged	Dog	>3 mg/kg	Single	Intravenous	*EMEA approval document:* Assessment Report (Page:23) PDF 4262k	2016
2	Palbociclib	Electrocardiogram QT prolonged	Dog	>10 mg/kg	Single	Intravenous	*EMEA 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

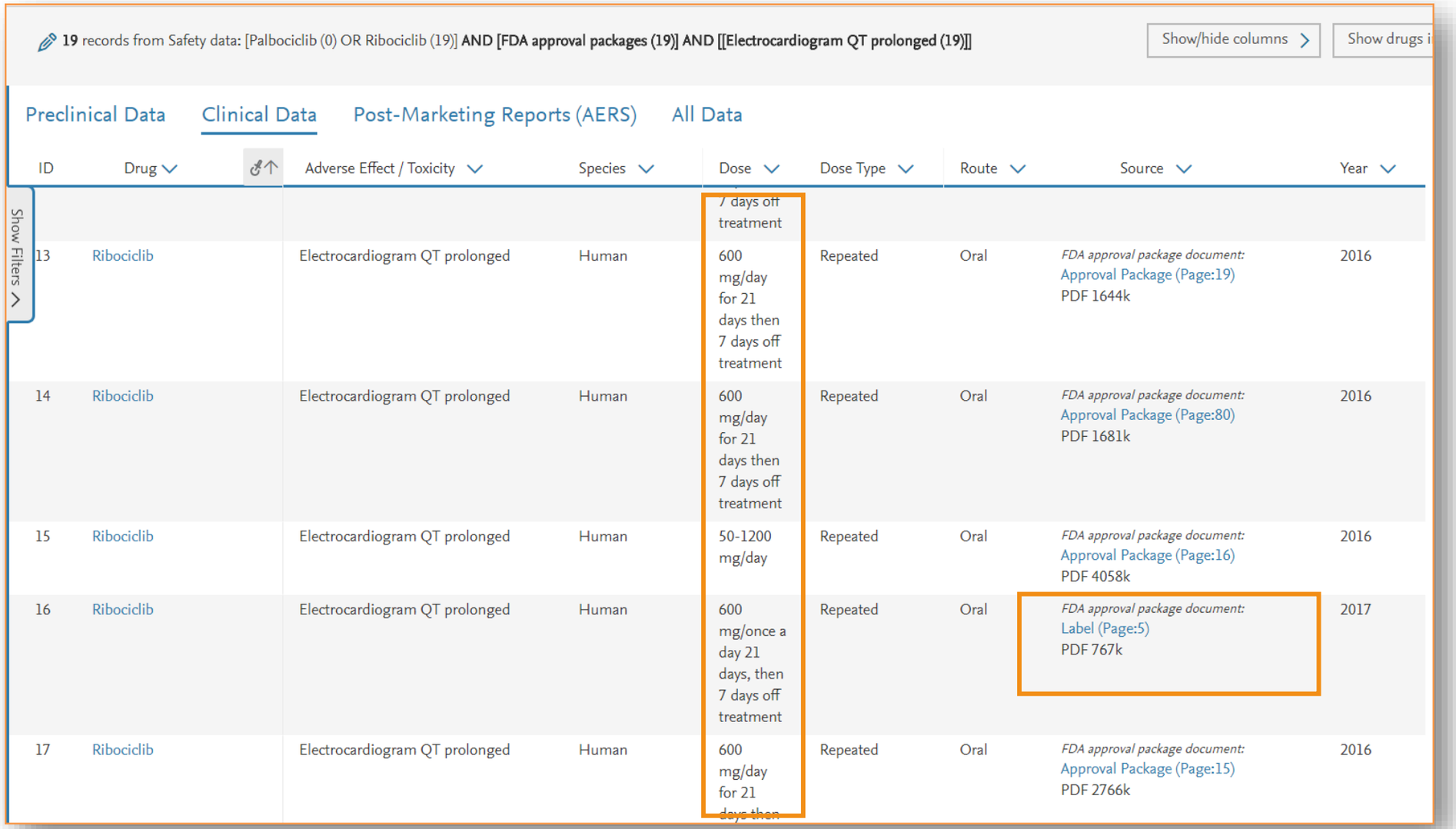
- 直接在原文中参考实验方法和结论



- 以动物模型‘dog’为基础的QT实验研究得出结论，可以对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

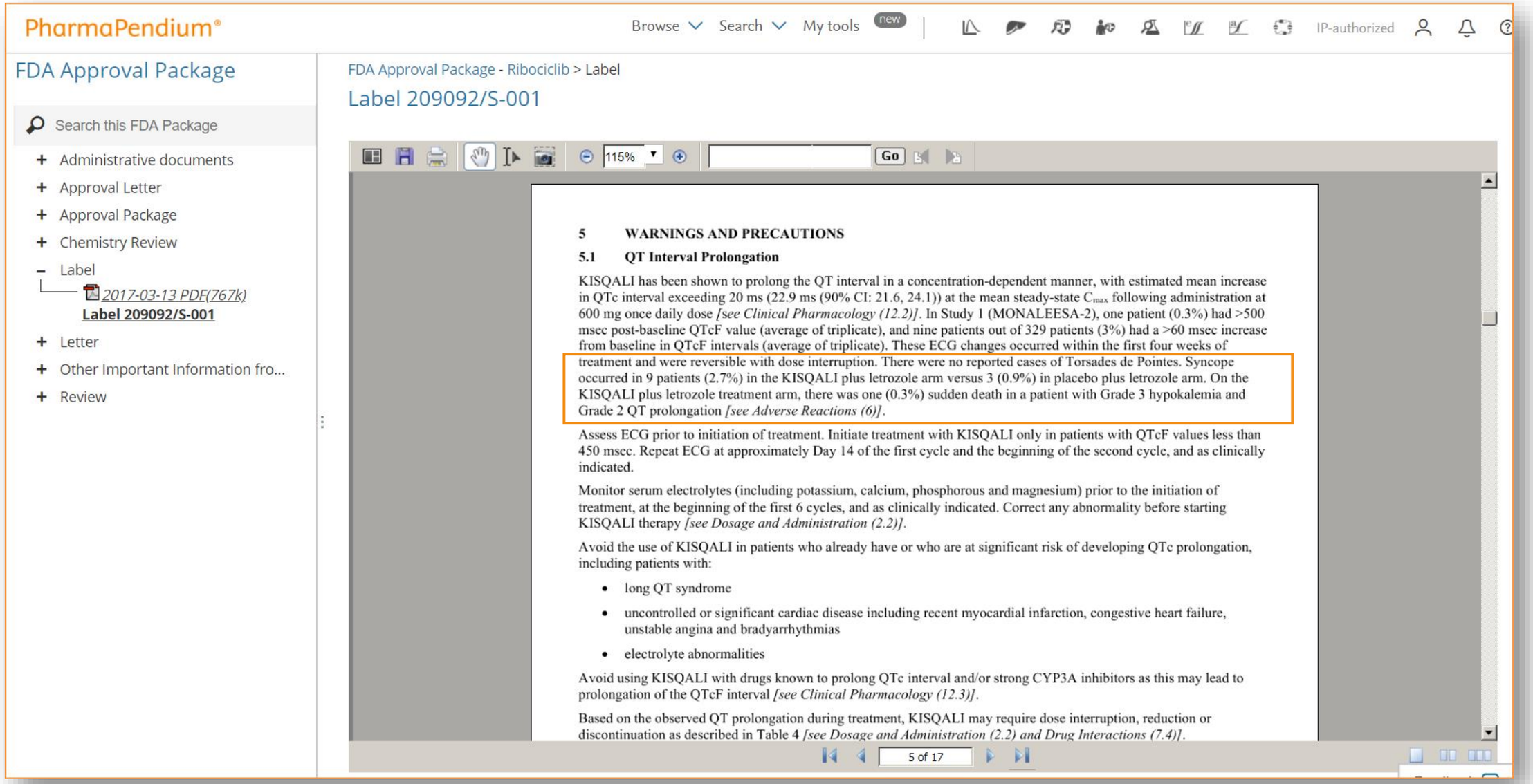
Preclinical Data | Clinical Data | Post-Marketing Reports (AERS) | All Data

Show Filters

ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
				7 days off treatment				
13	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: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

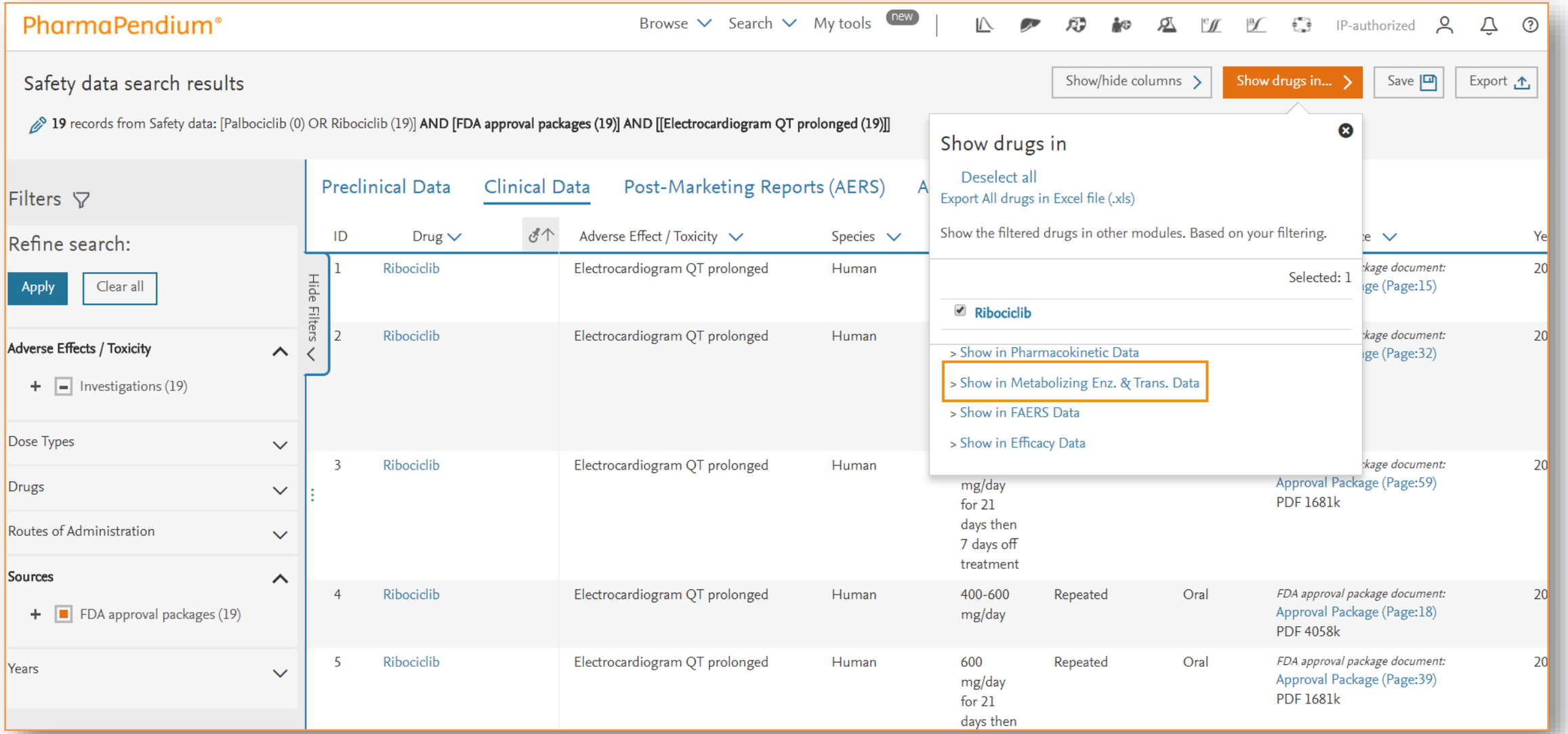
FDA----Safty---临床前毒理研究

- 该药的标签中，得到明确的关于Ribociclib的QT毒副作用的描述

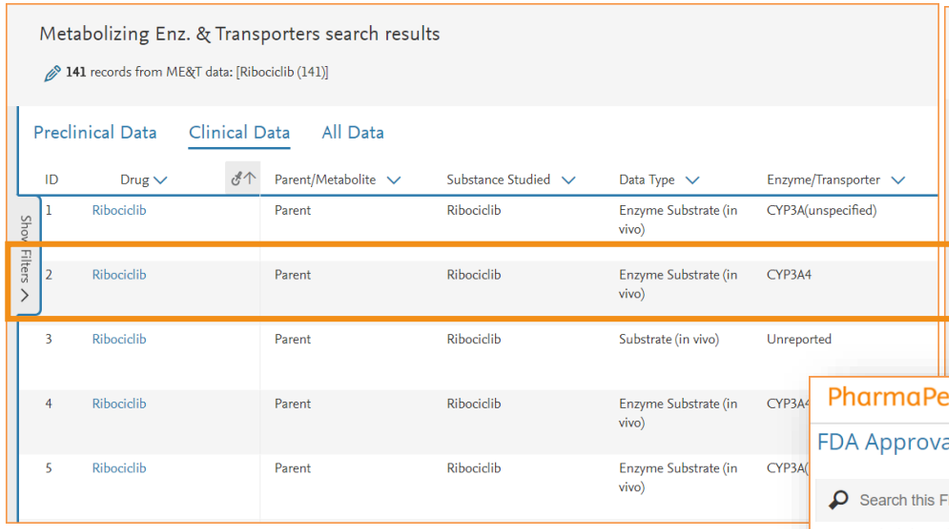


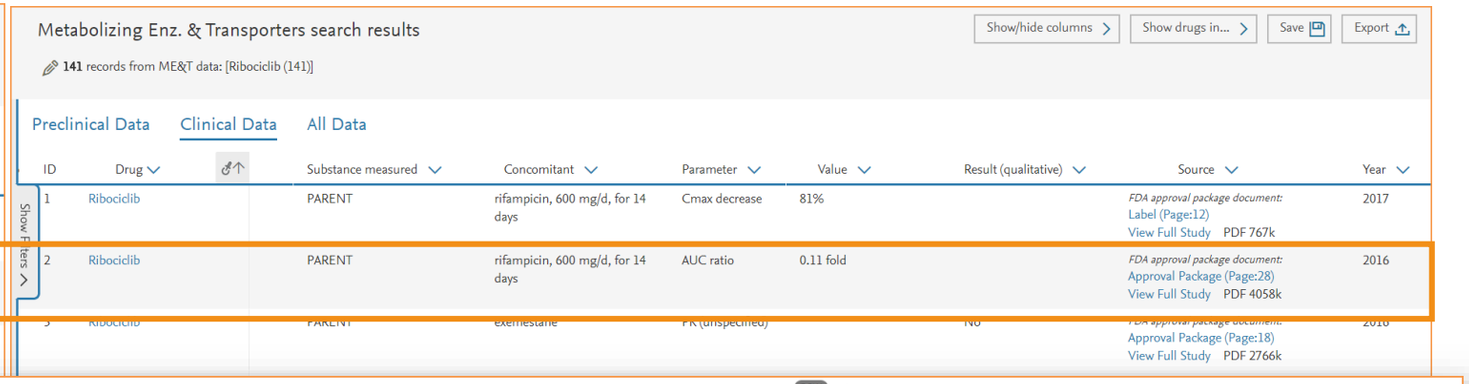
FDA----Safty---临床前毒理研究

- 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

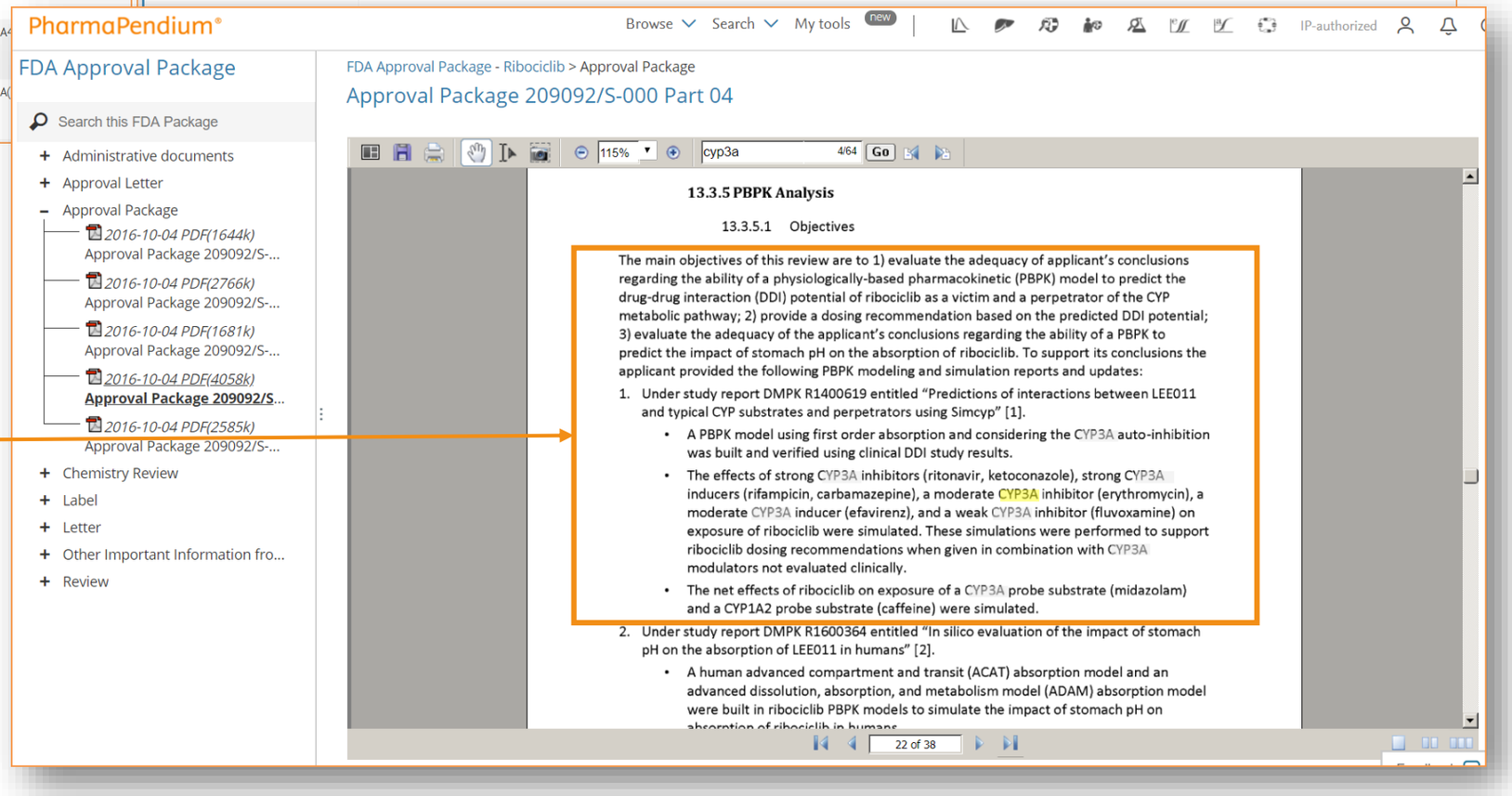


FDA----Safty---临床前毒理研究





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



Case study: Elsevier 与Novartis 进行深度合作，利用Pharnapendium预测药物临床前的安全性

Accessing Marketed Drug Information from PharmaPendium to Inform PreClinical Safety

Duncan Armstrong
Preclinical Secondary Pharmacology, Novartis

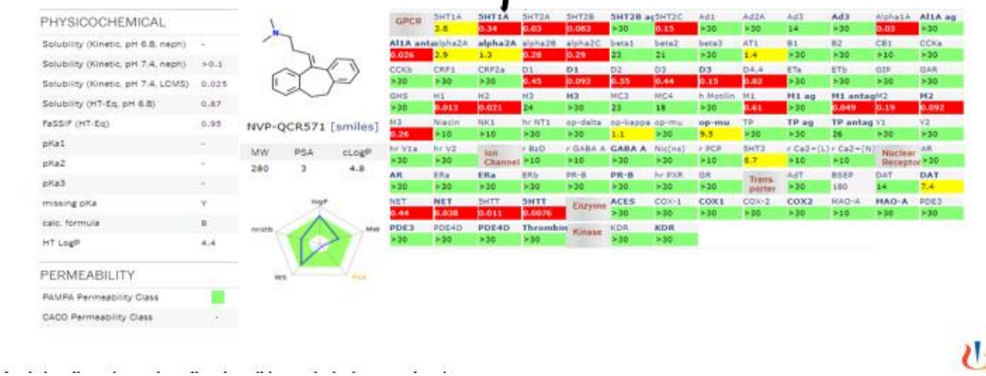
Pooja Jain
Product Manager, PharmaPendium, Elsevier

ELSEVIER

NOVARTIS

Screening alone is insufficient to quantify safety risk

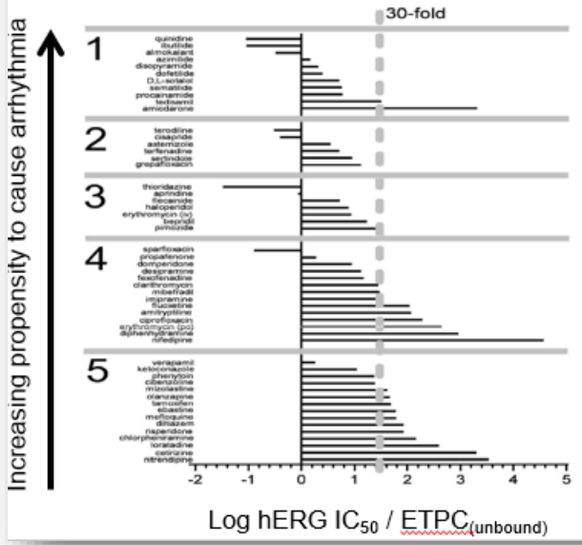
To determine whether or not in vitro activity will translate in to a clinical risk requires an understanding of how much off-target engagement is required to drive an adverse event



NOVARTIS

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

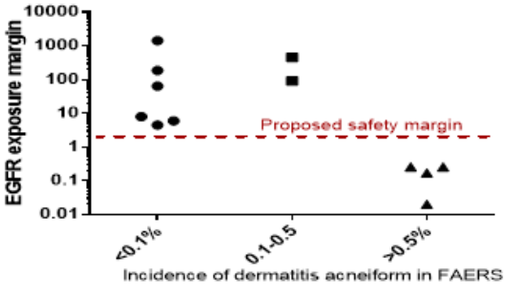
$$\text{Safety Margin} = \frac{\text{In vitro IC50}}{ETPC_{(unbound)}}$$

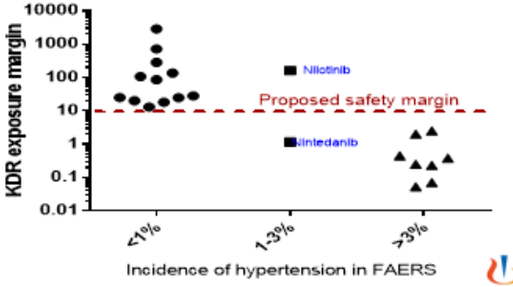
IMPACT: simple, rapid, inexpensive in vitr
assay routinely implemented in early disc
Molecules with poor safety margin are de

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

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}/free Cmax] were estimated to be 2 for EGFR and 10 for KDR





NOVARTIS

药效（Efficacy）：糖尿病替代临床终点信息检索

Empowering Knowledge

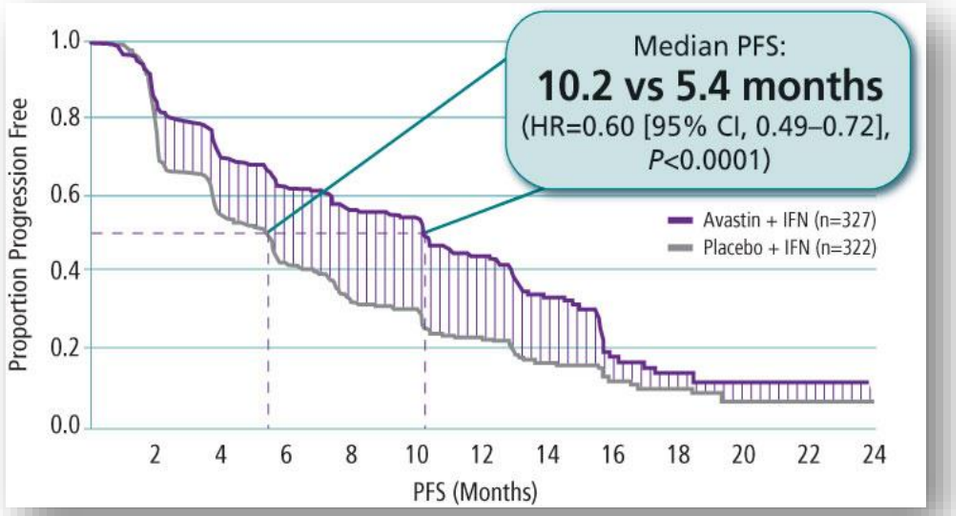
Efficacy信息检索

- 什么是药效（Efficacy），临床终点（endpoints）

药效（Efficacy）：
- 在研药物到达研发预期，相较与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

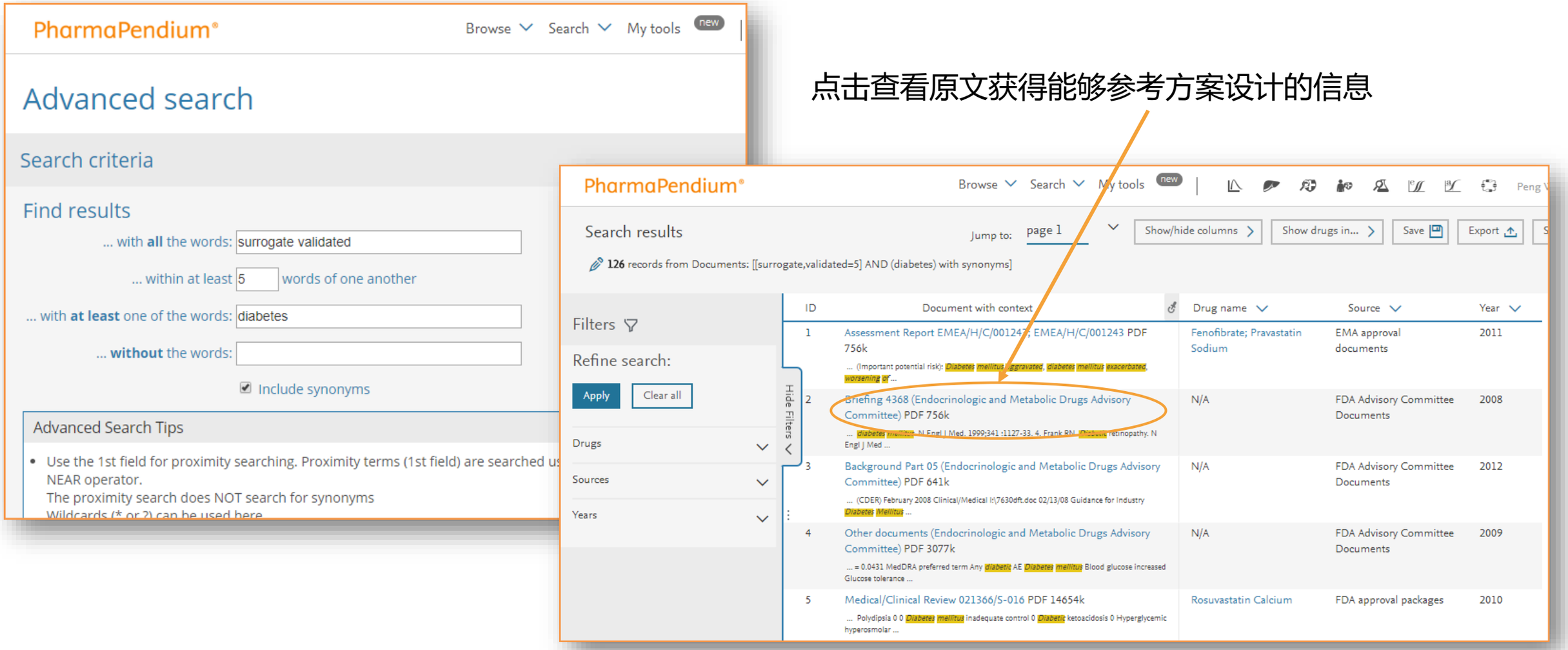
- 替代临床终点：

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

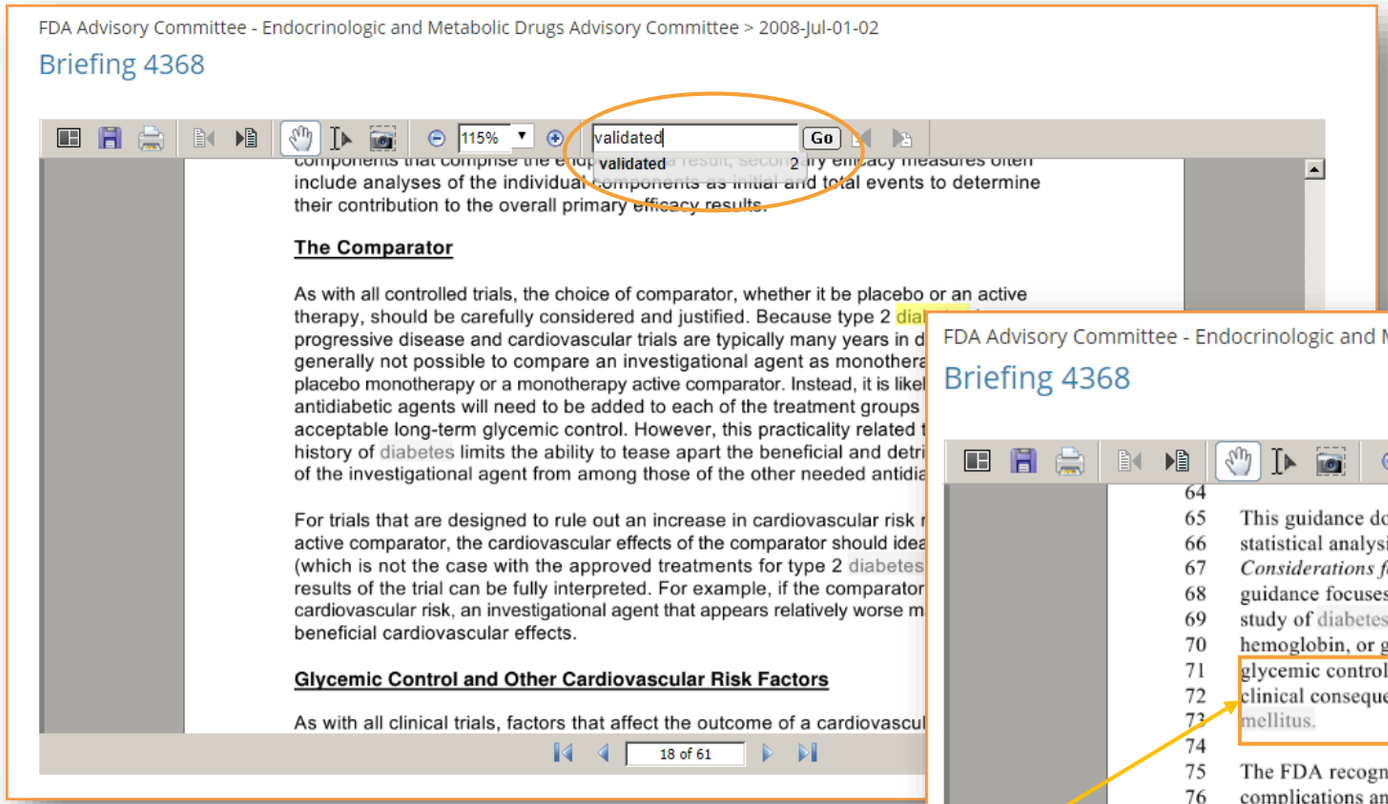
Validated Surrogate Endpoint	Correlated Clinical Outcome
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) *The amount of air that a person can blow out of his or her lungs in 1 second*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

Efficacy----替代临床终点相关信息检索

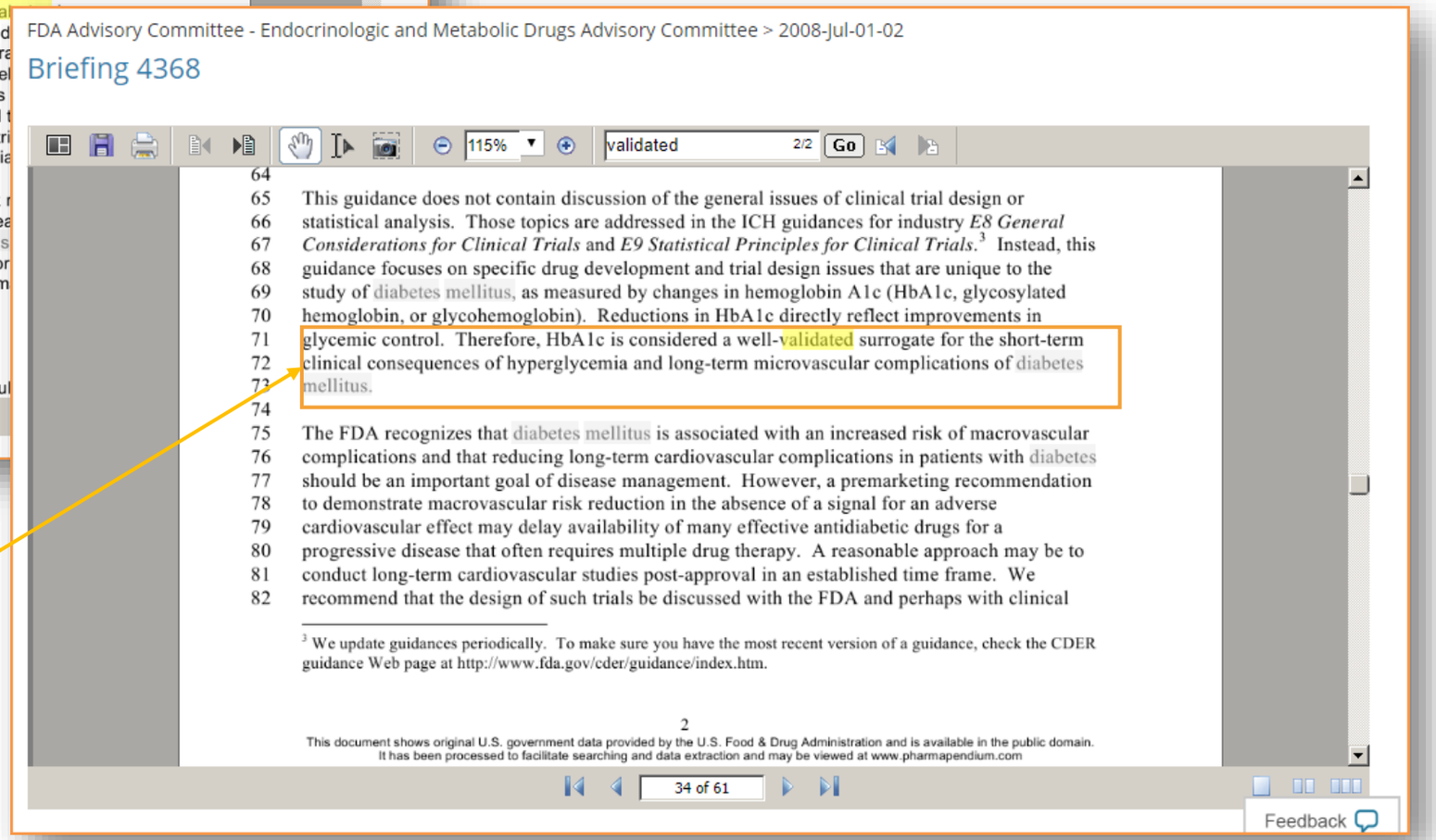
- 检索，糖尿病的临床替代终点信息（validated surrogate and unvalidated surrogate）



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

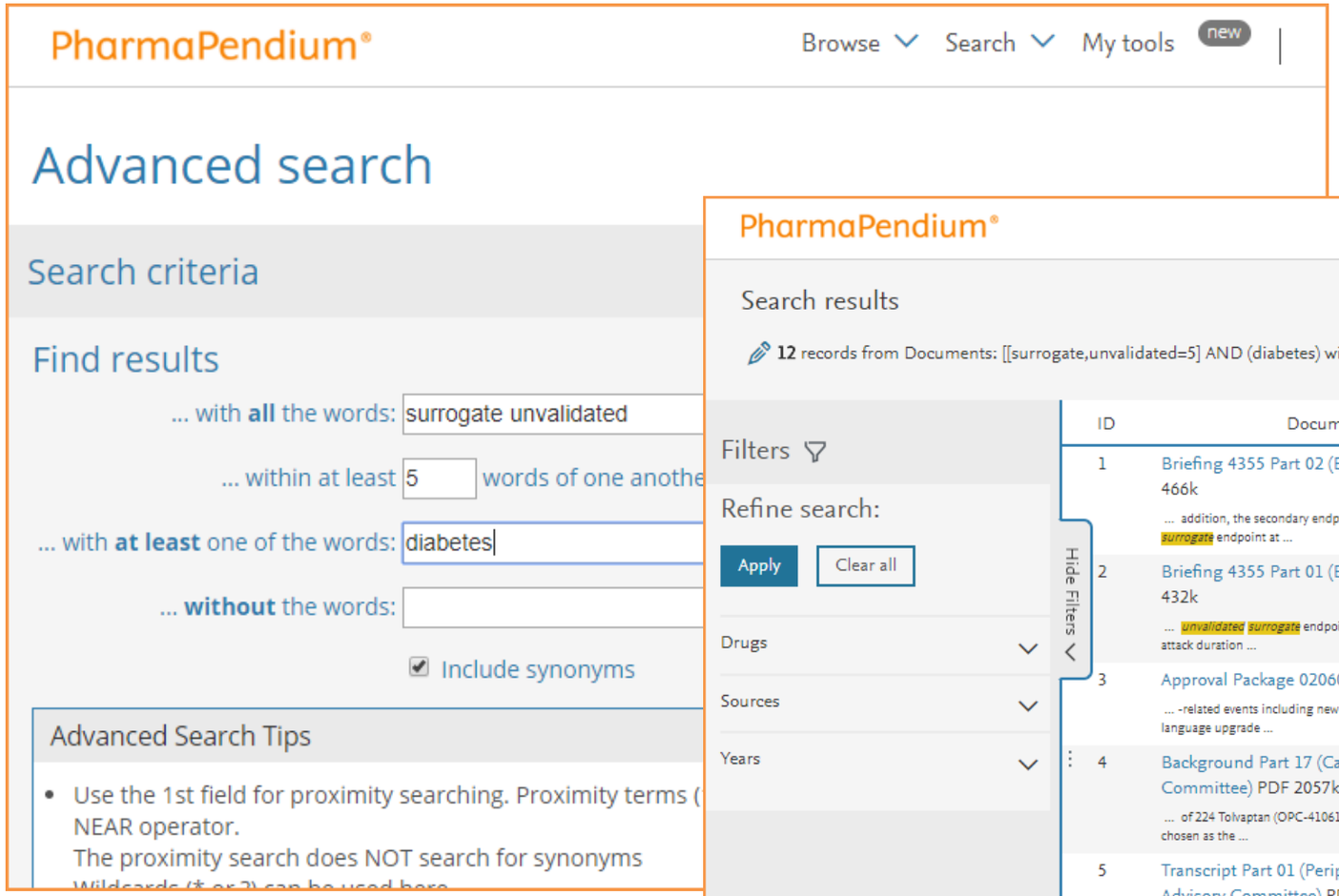


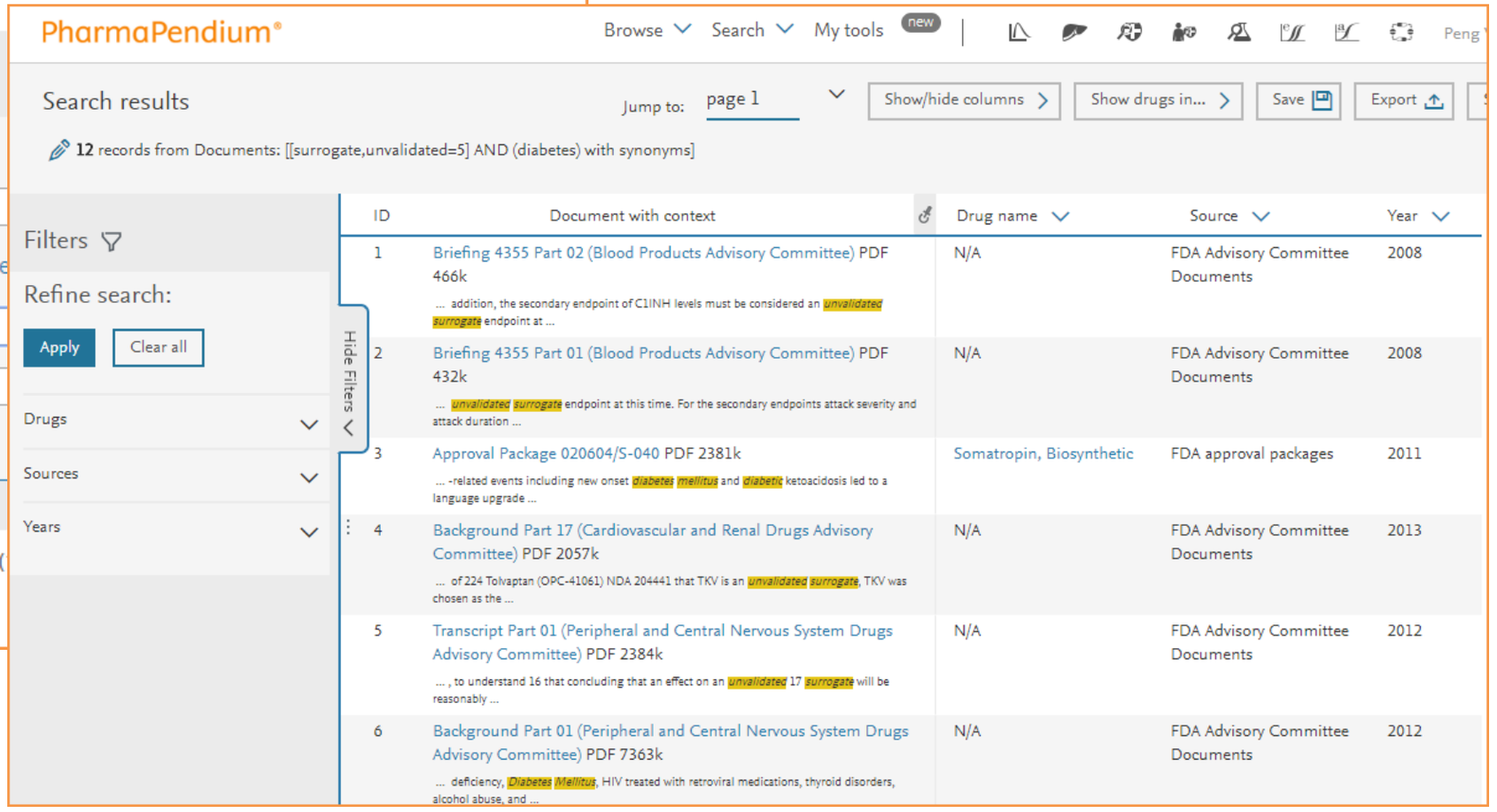
- 在原文上直接进行‘text searching’锁定准确位置



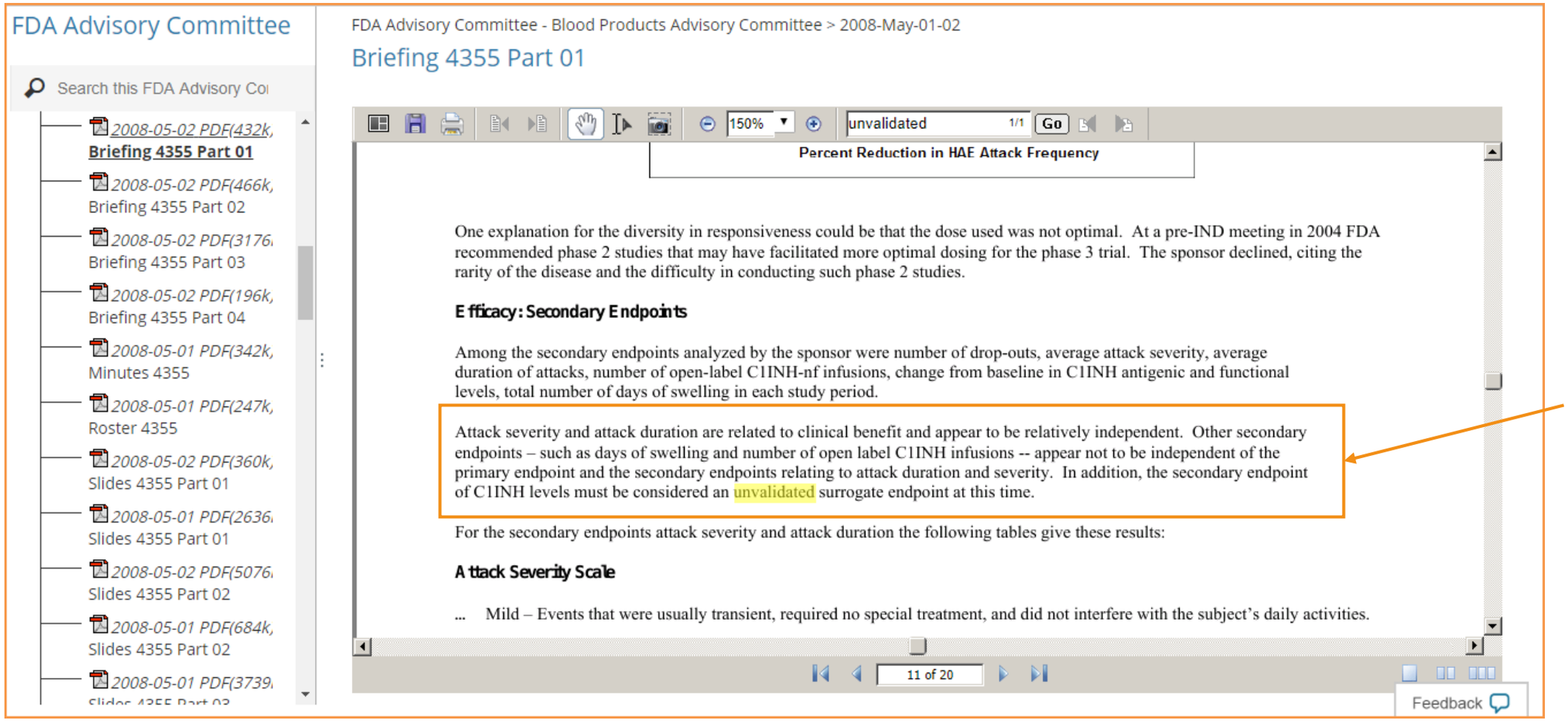
HbA1c被认为是well-validated替代终点.....

Efficacy------unvalidated surrogate信息检索





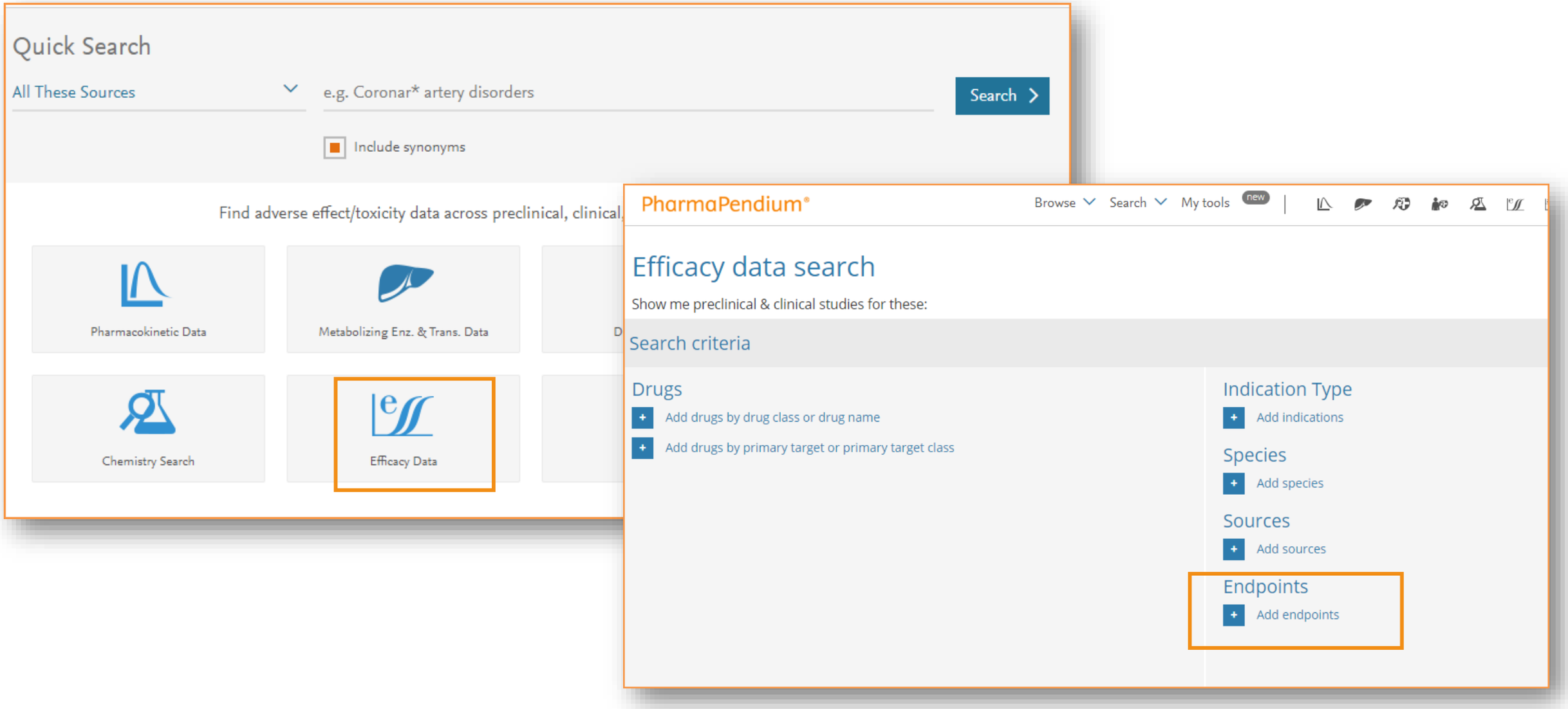
Efficacy—临床终点原文信息快速定位



- .....二级终点应当被认为是unvalidated的替代终点

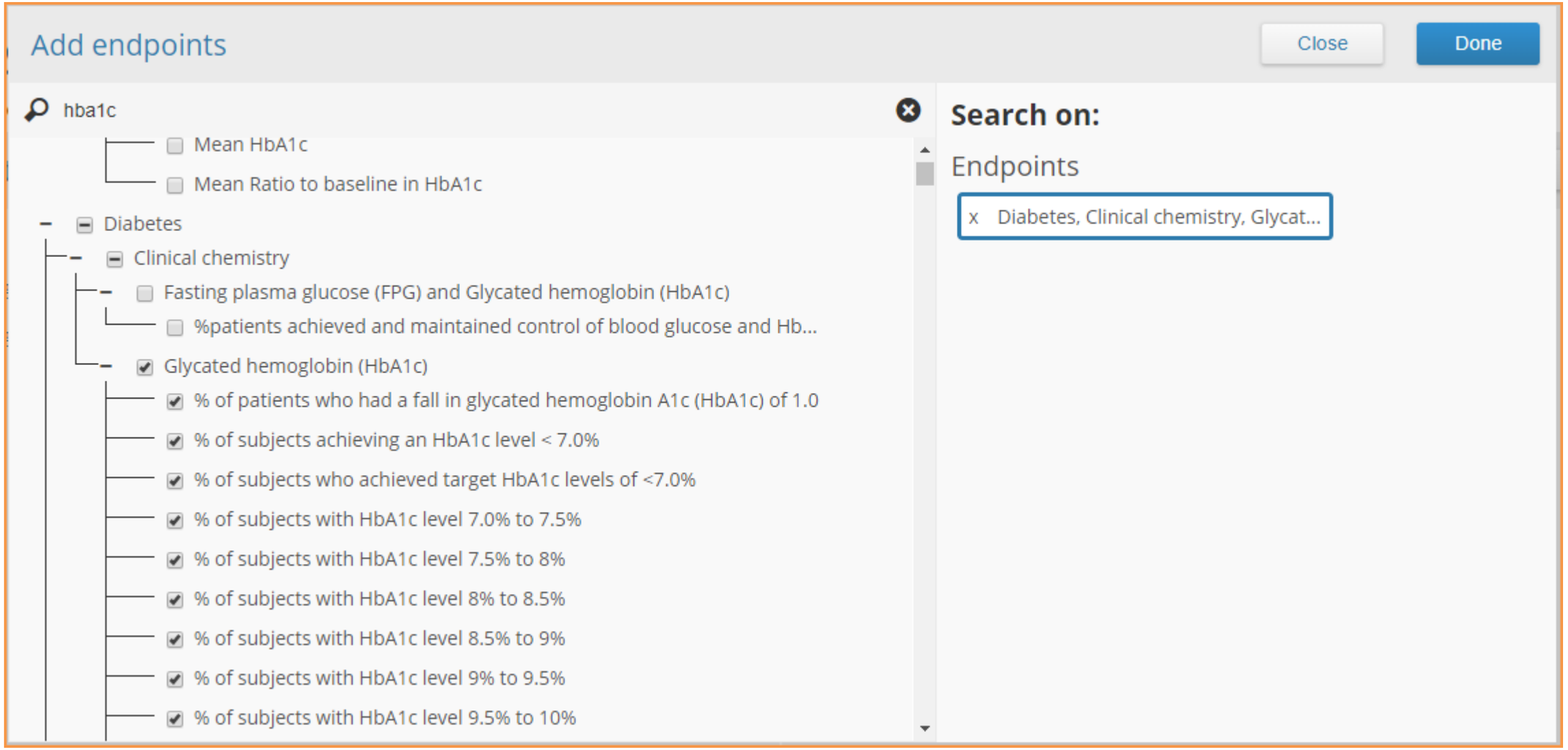
Efficacy---临床终点信息总览

- 需要收集‘diabetes’全部临床终点信息时



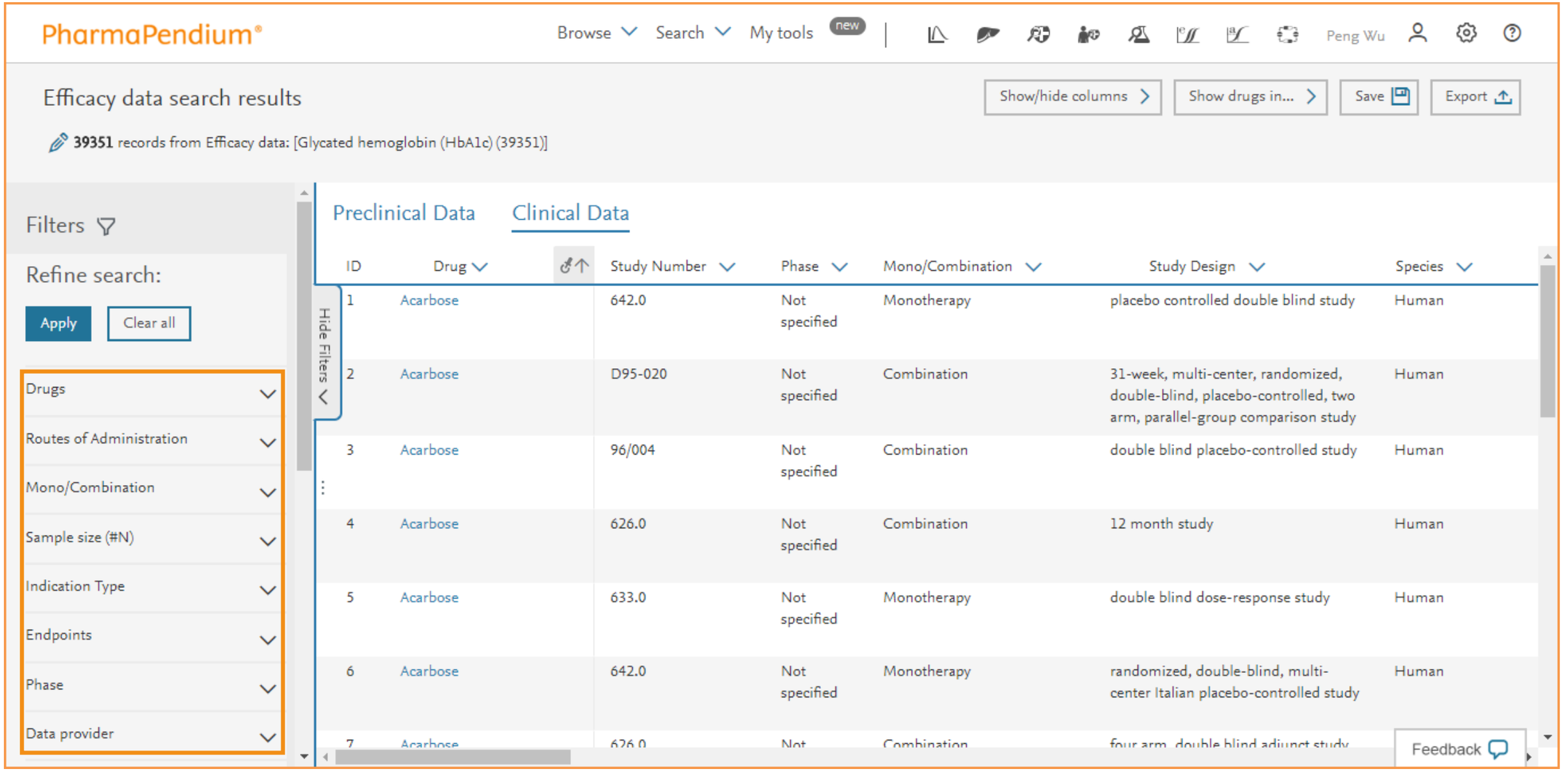
Efficacy---临床终点信息总览

- 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

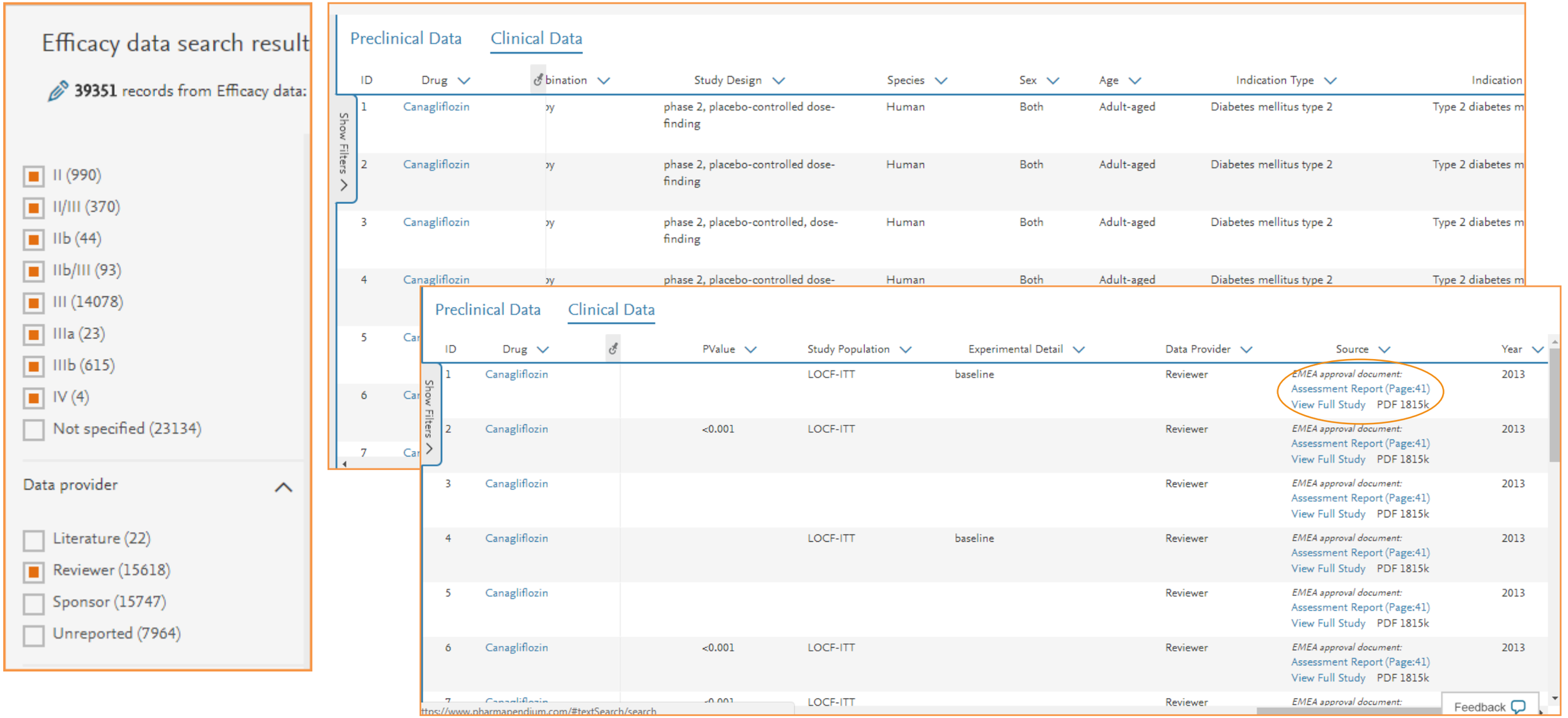


Efficacy---临床终点信息总览

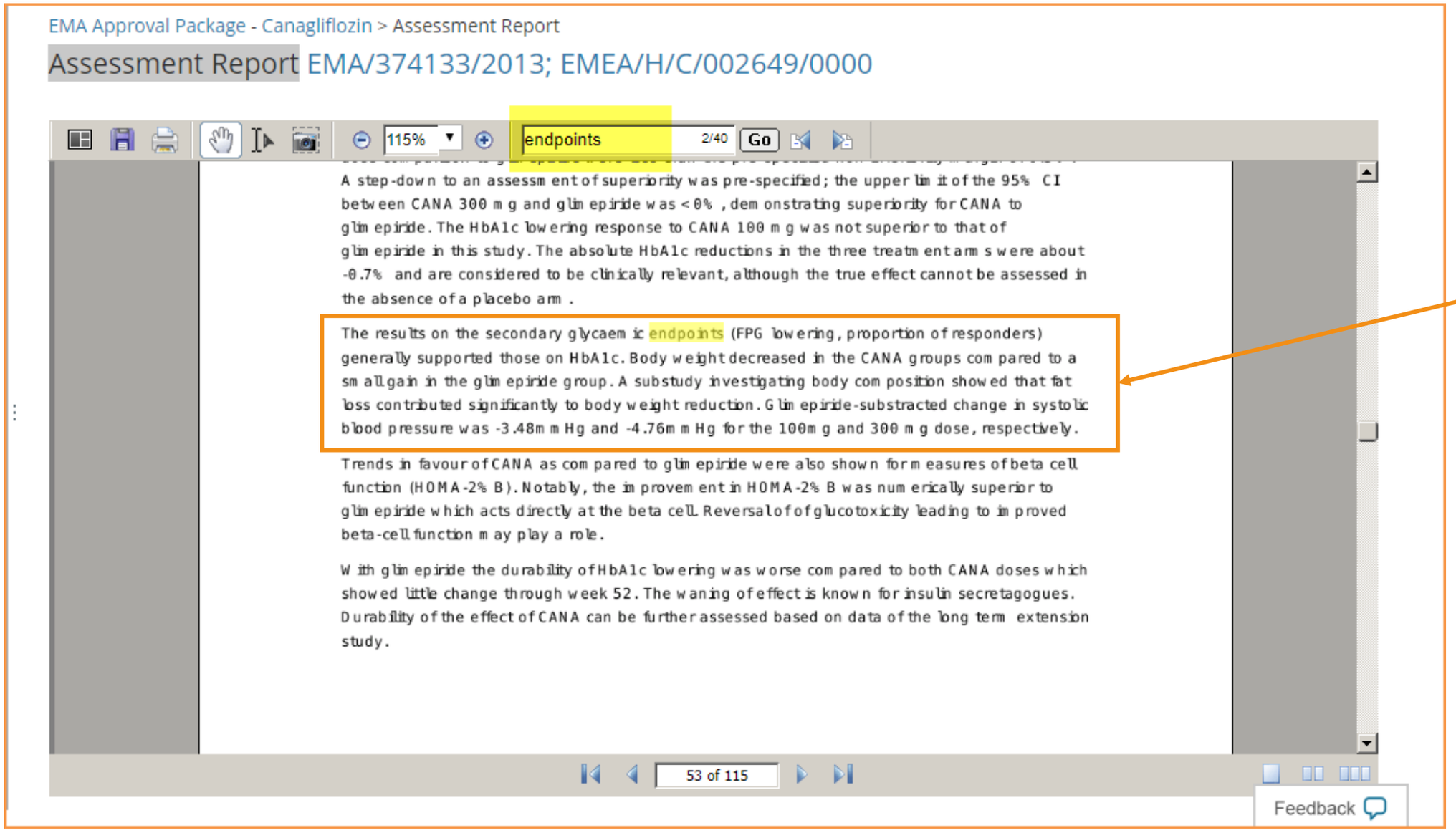
- 对感兴趣的内容进行进一步的筛选：如，找到phase II, III等明确的临床终点信息



Efficacy---临床终点信息总览



Efficacy---临床终点信息总览



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

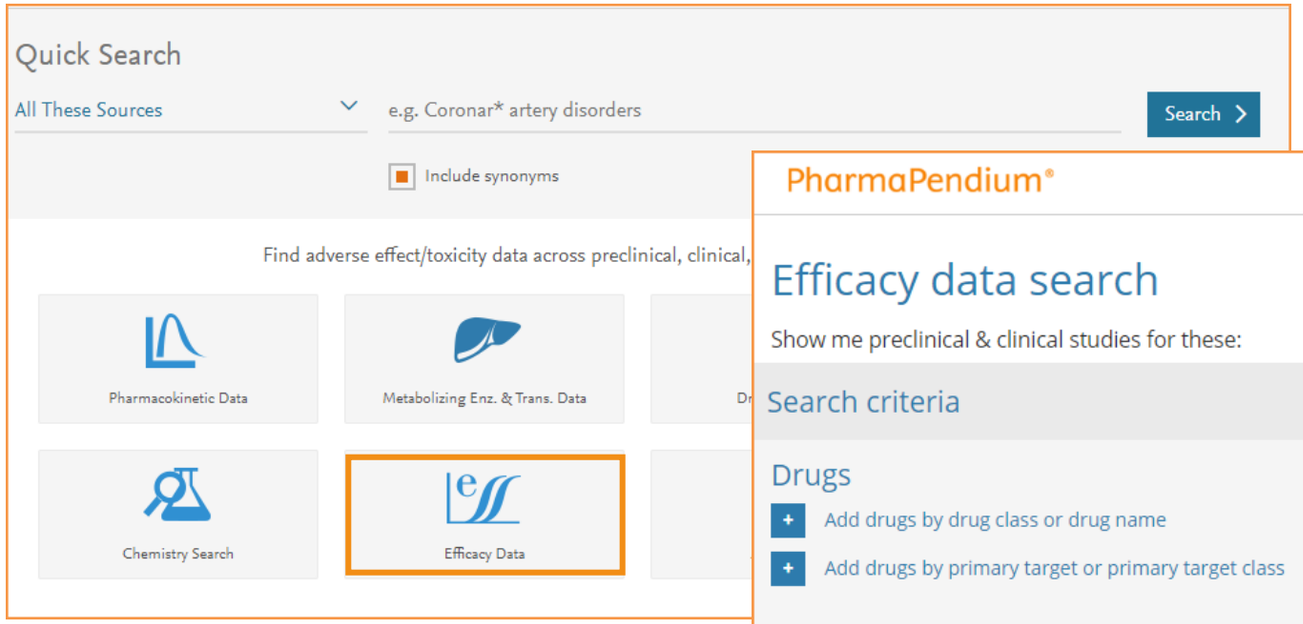
药效：非小细胞肺癌安慰剂组相关信息检索

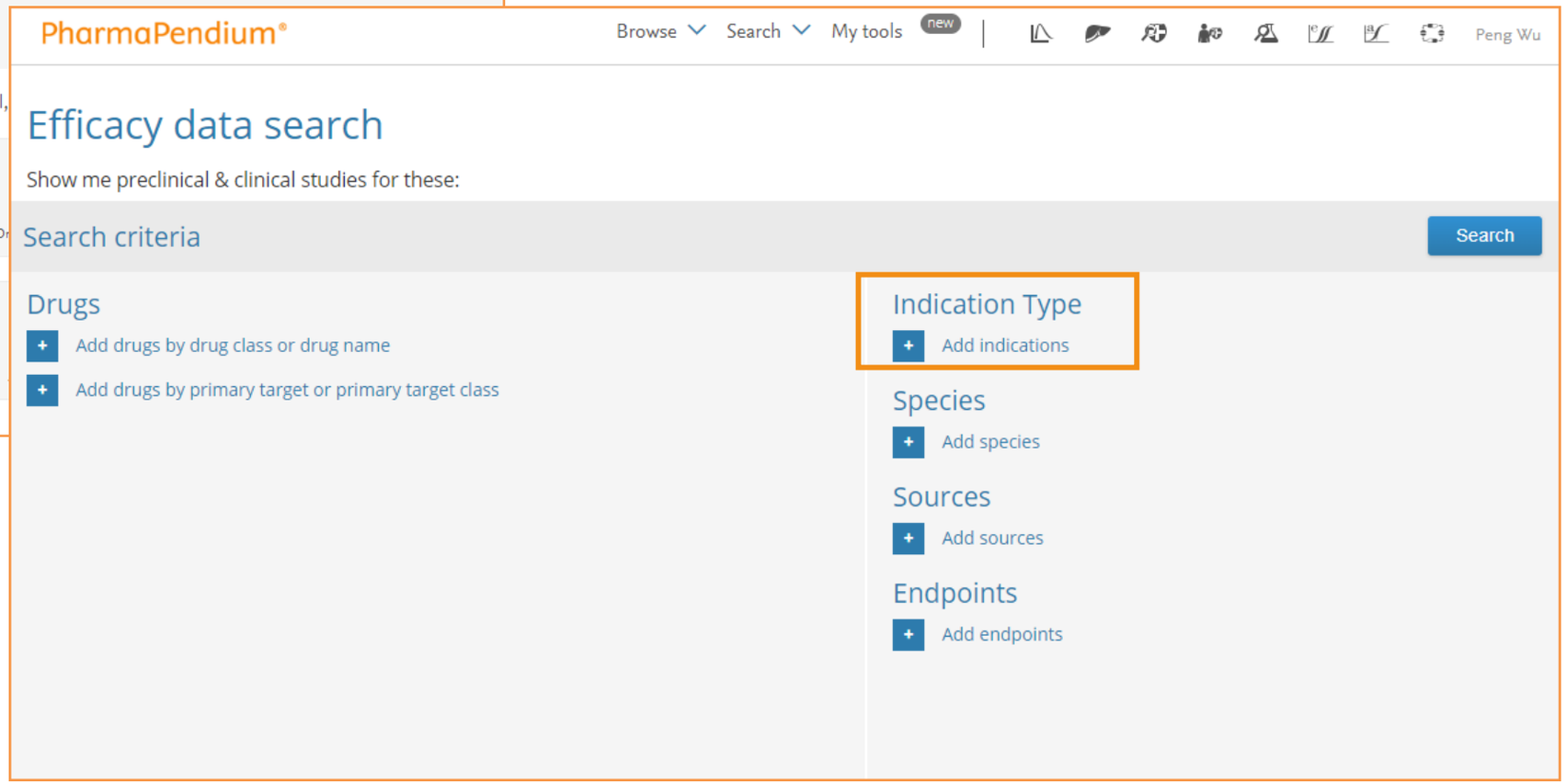
ELSEVIER

Empowering Knowledge

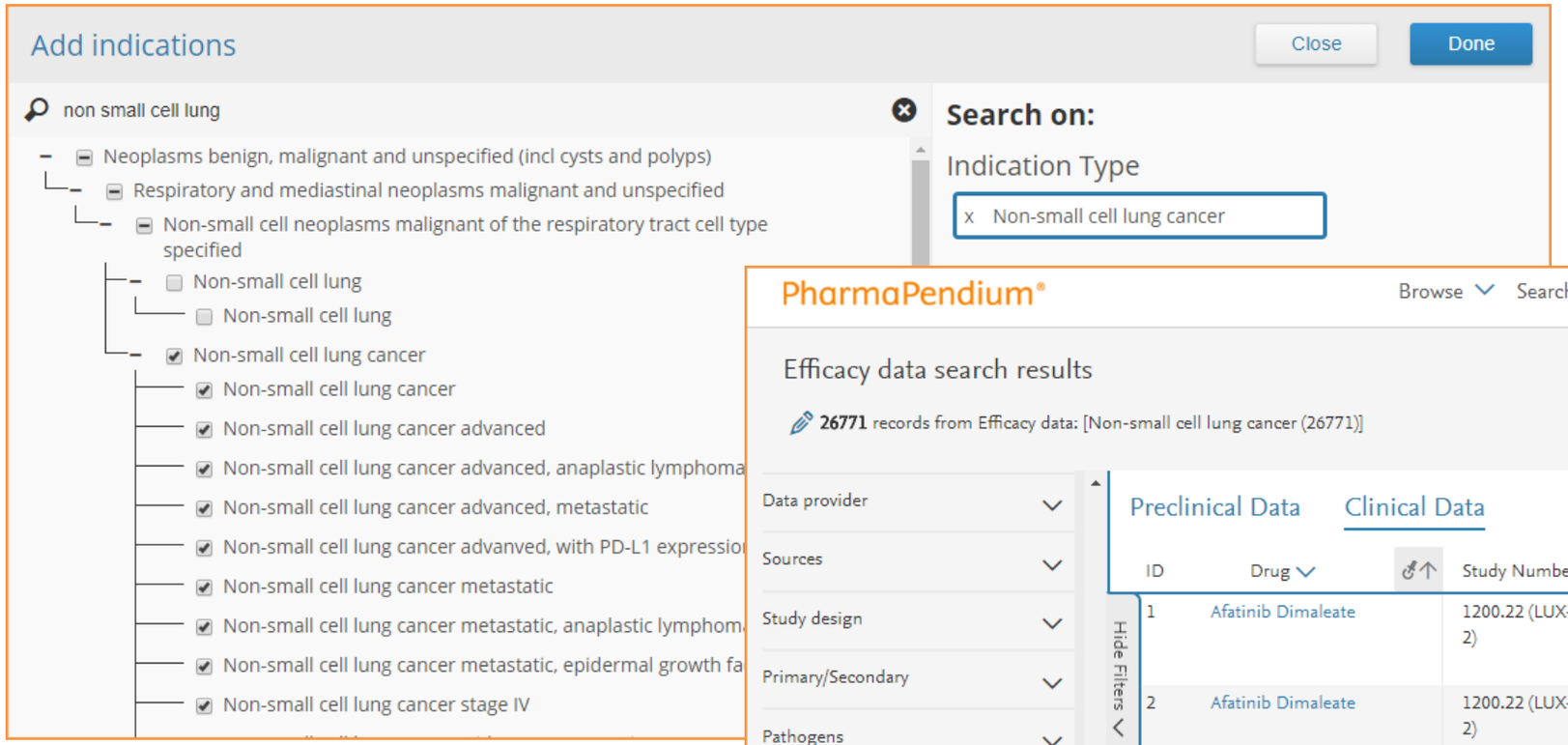
Efficacy----安慰剂组临床信息检索

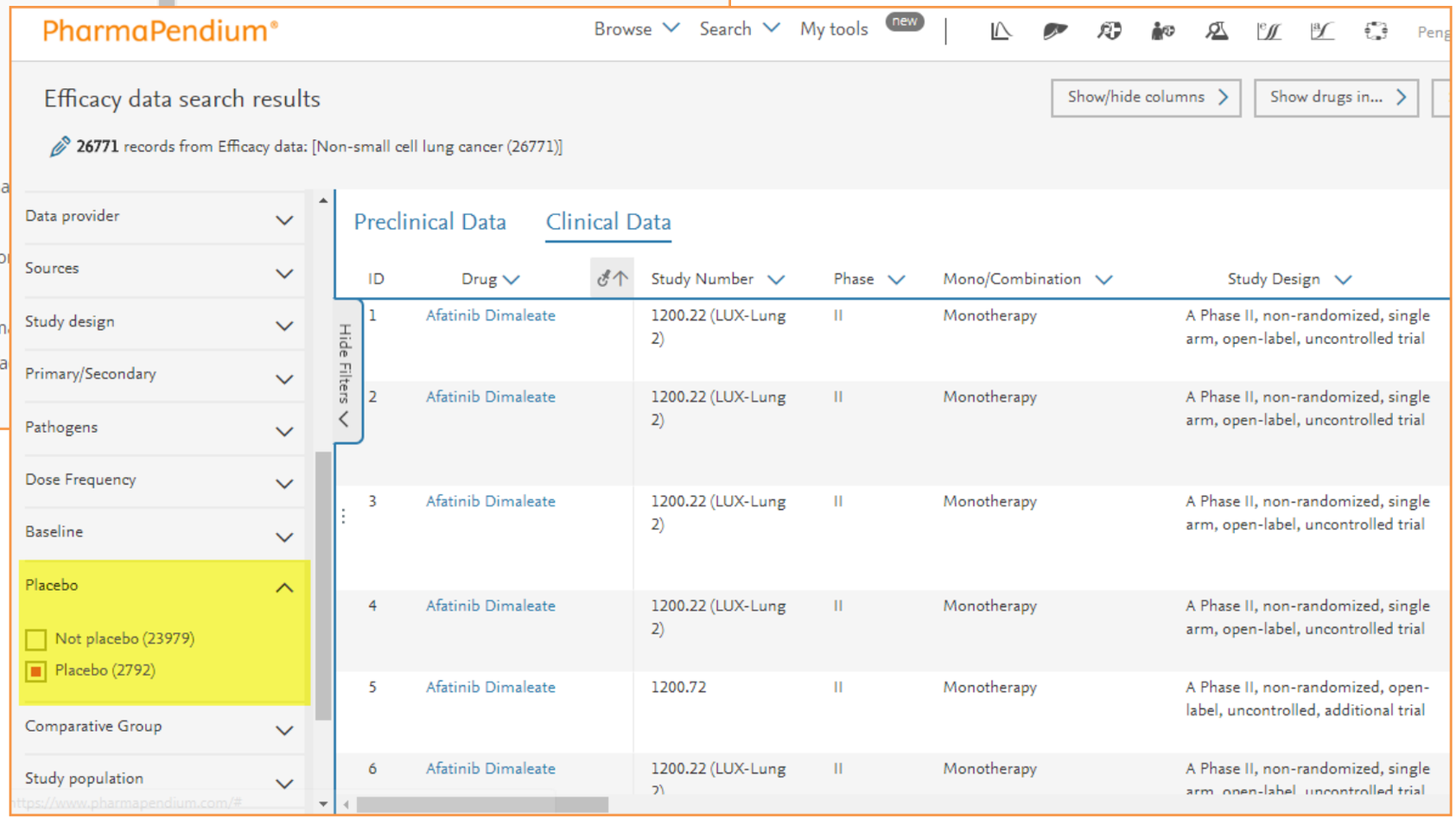
- 在进行临床方案设计和决策时，如何快速根据适应症收集特定的临床经验来辅助决策，提高效率？如：检索已有的NSCLC安慰剂效应相关临床研究





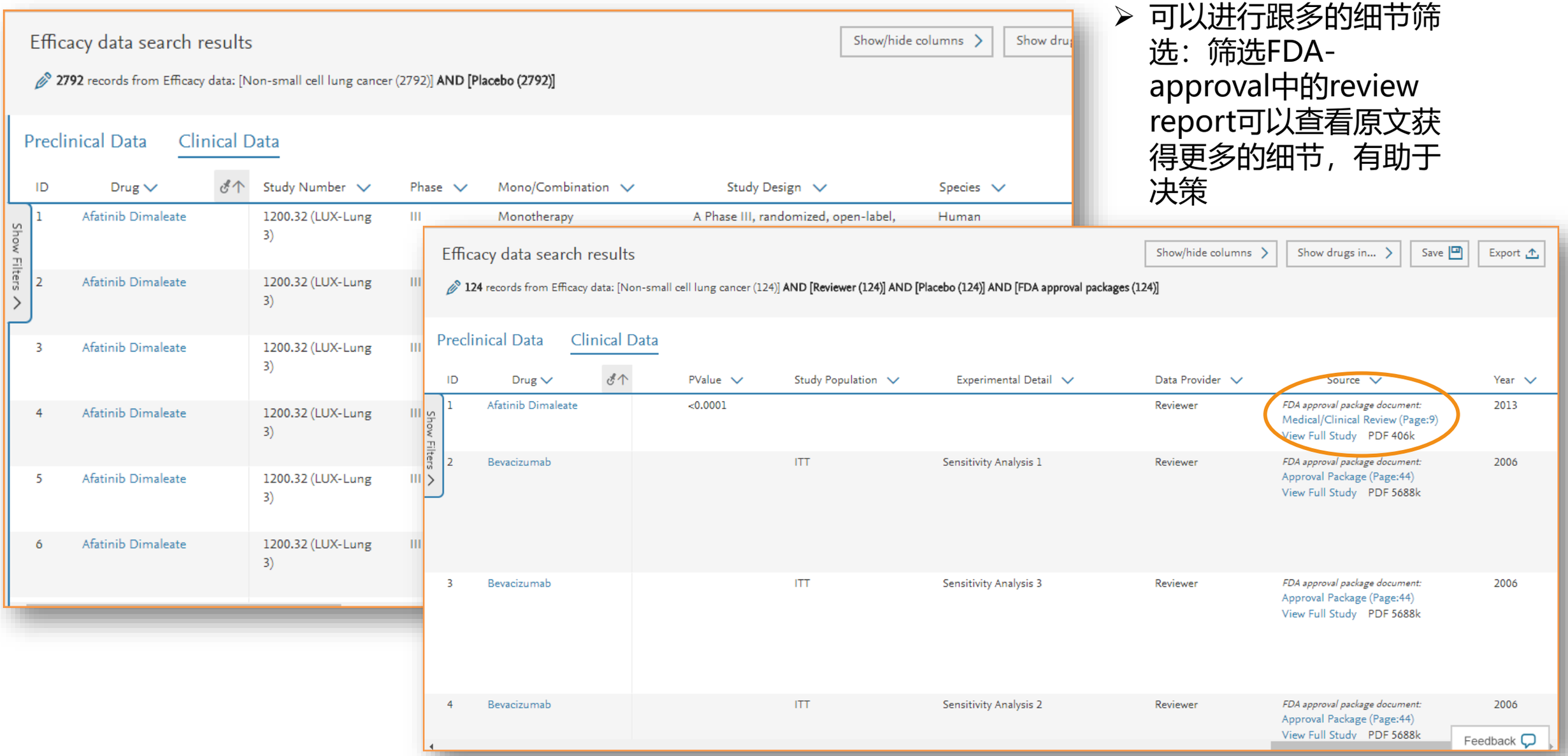
Efficacy----安慰剂组临床信息检索





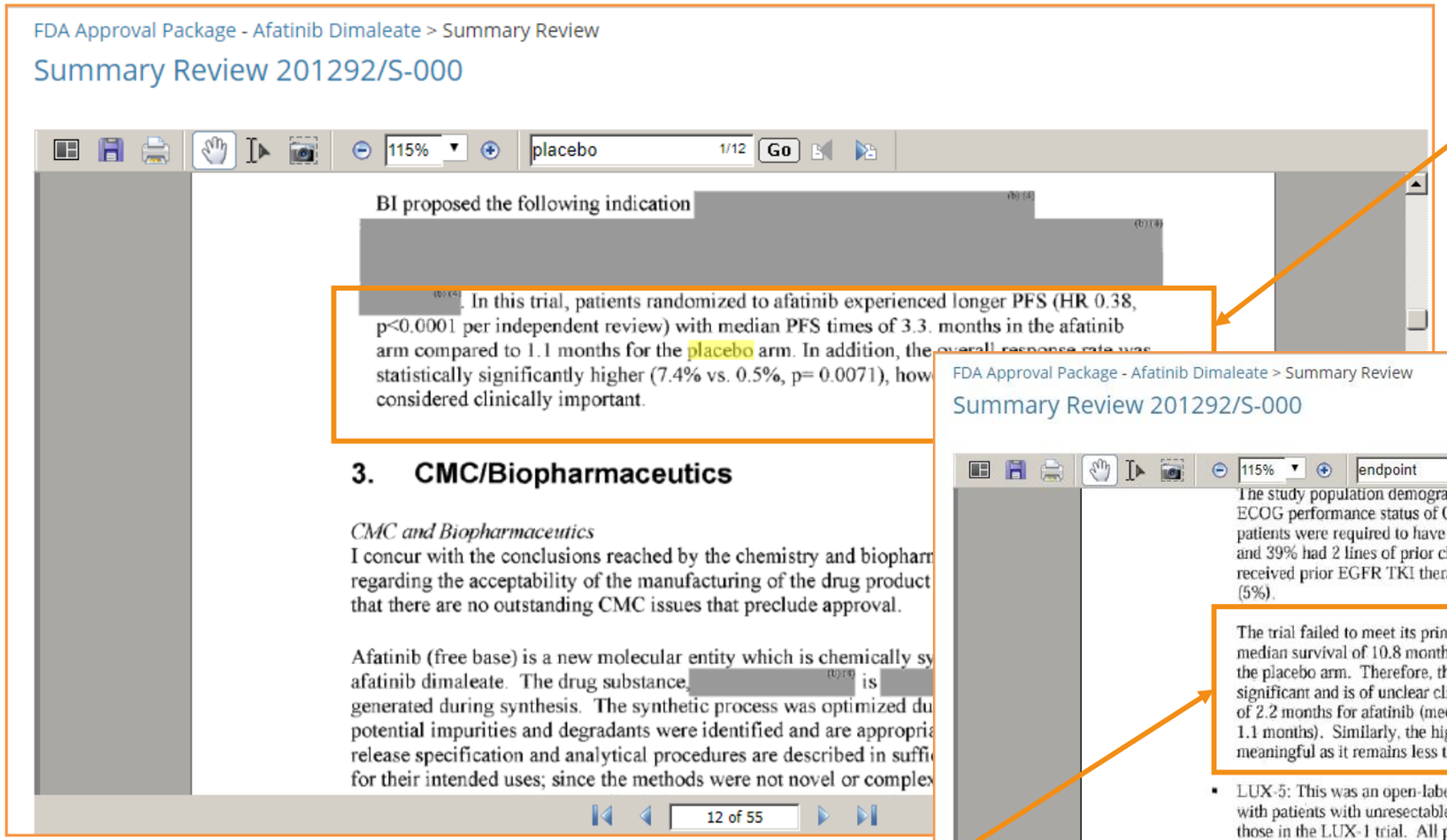
- 结果集中直接筛选 ‘安慰剂’得到以适应症为基础的安慰剂效应研究总览表

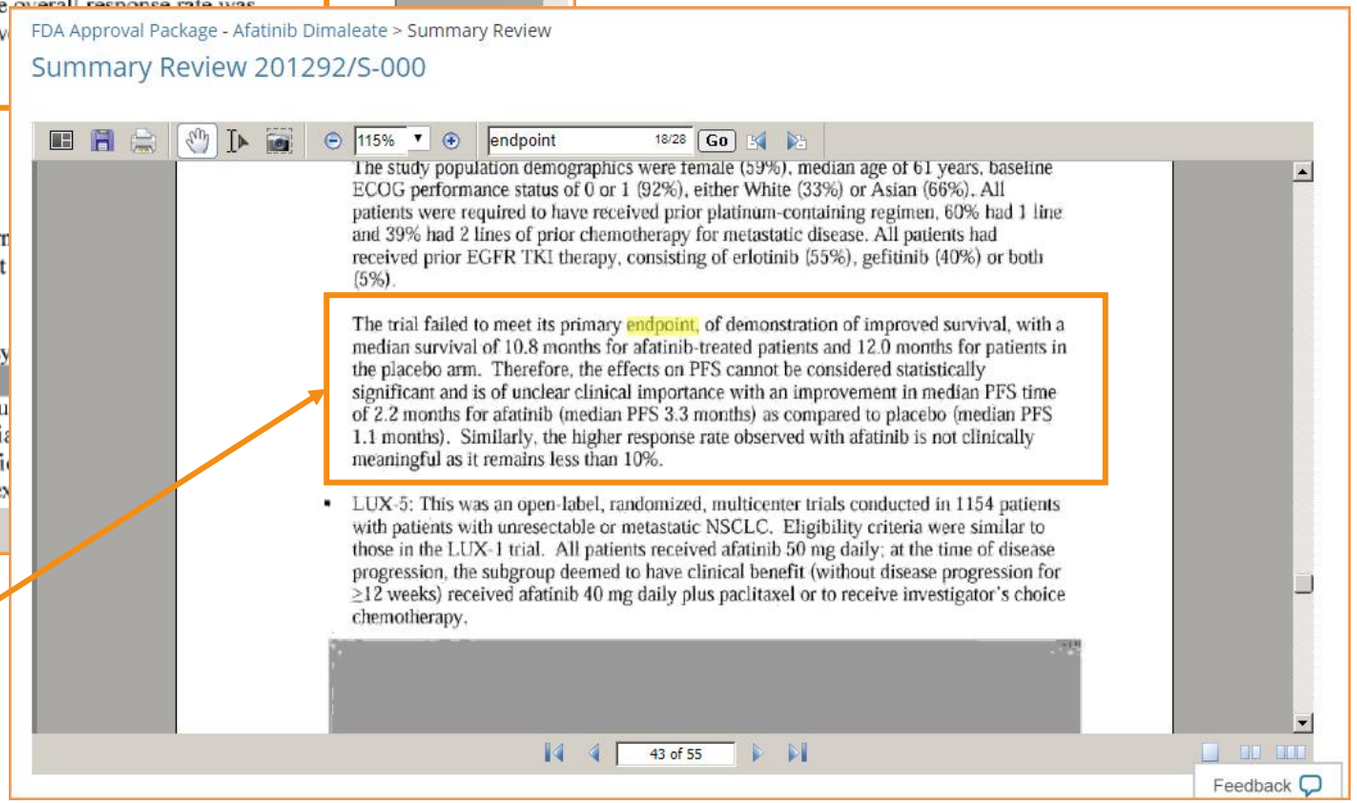
Efficacy



- 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





- 安慰剂组与非安慰剂组的临床结果对比

- 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

ELSEVIER

Empowering Knowledge

Pharmacokinetic

- 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).

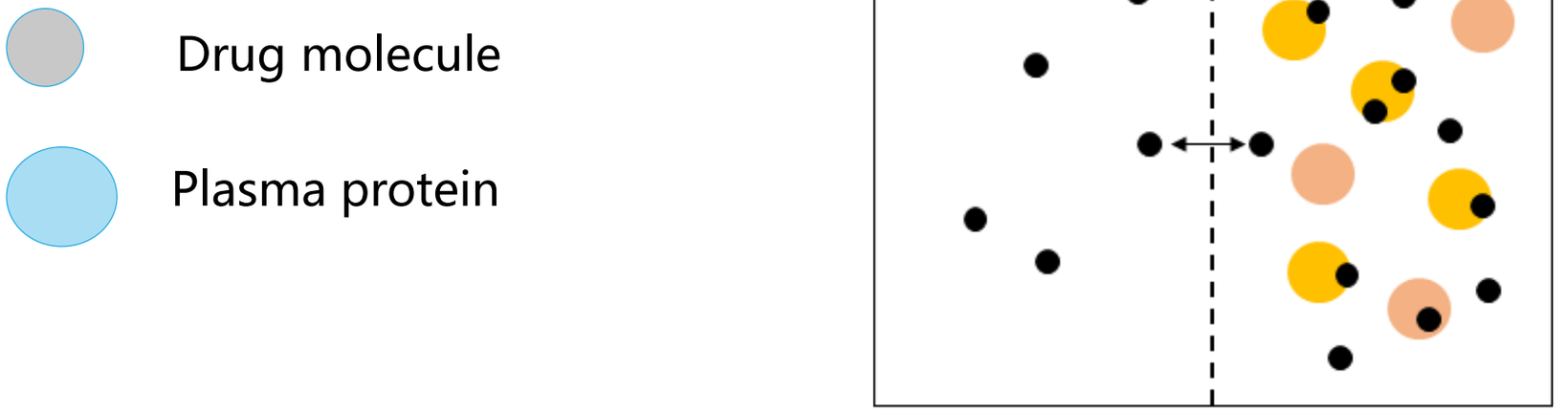
Factors that could influence the choice of the most appropriate species rather than the default to the most sensitive species include: (1) differences in the absorption, distribution, metabolism, and excretion (ADME) of the therapeutic between the species, and (2) class experience that may indicate a 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 fac
relevant recep
Preclinical S

When determ
distribution, and elimination parameters will not be known for humans. Comparative

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.

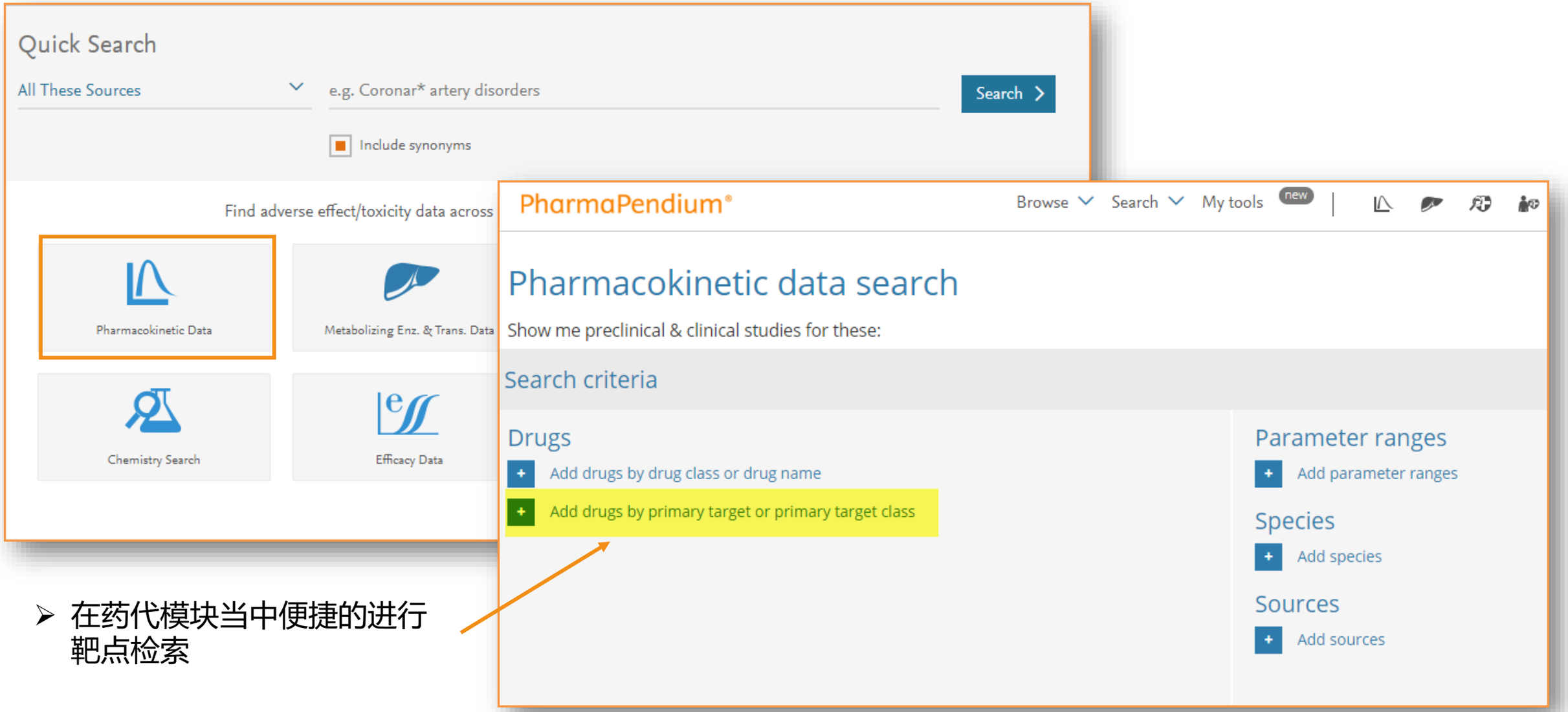
Pharmacokinetic

- 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。



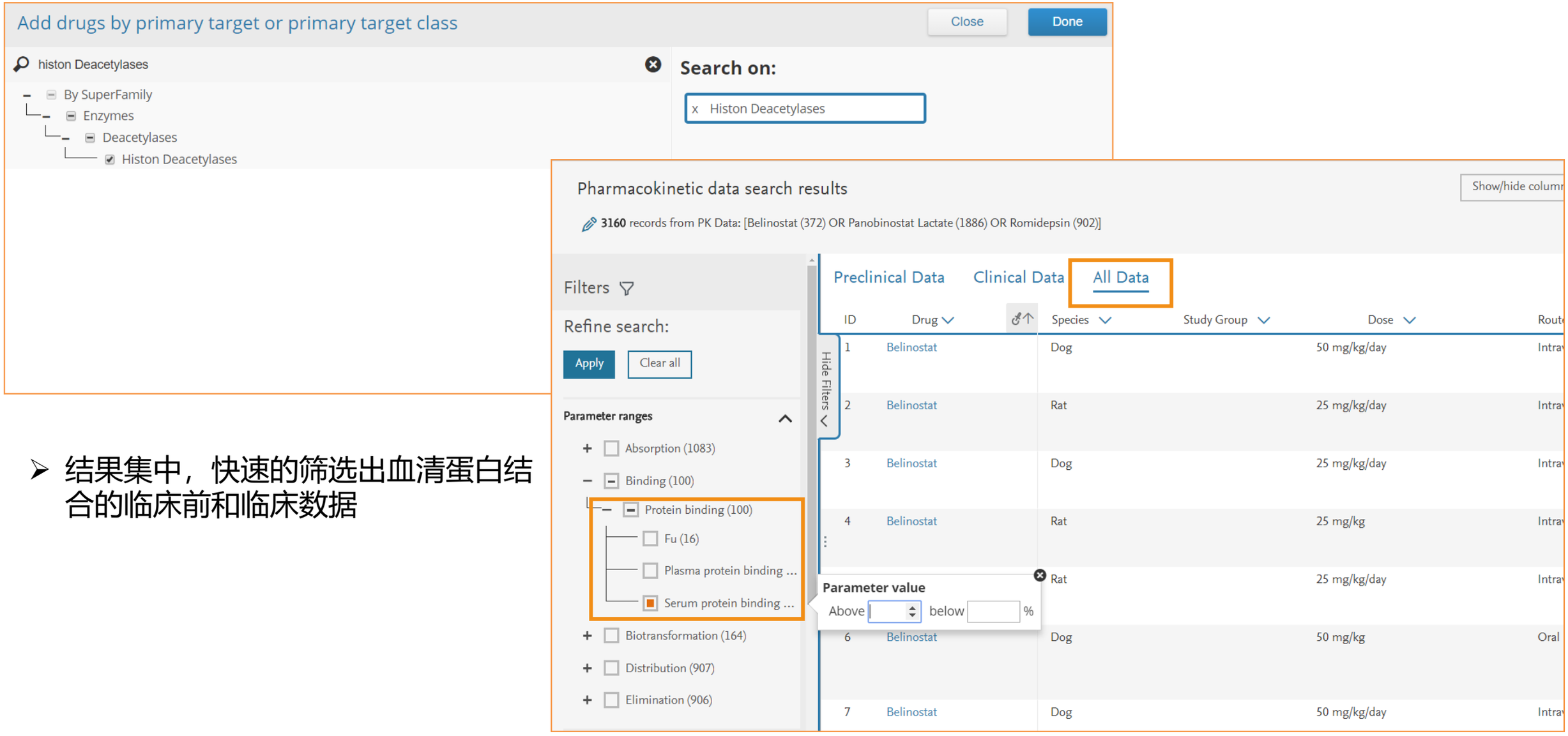
Pharmacokinetic

- 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



- 在药代模块当中便捷的进行靶点检索

Pharmacokinetic

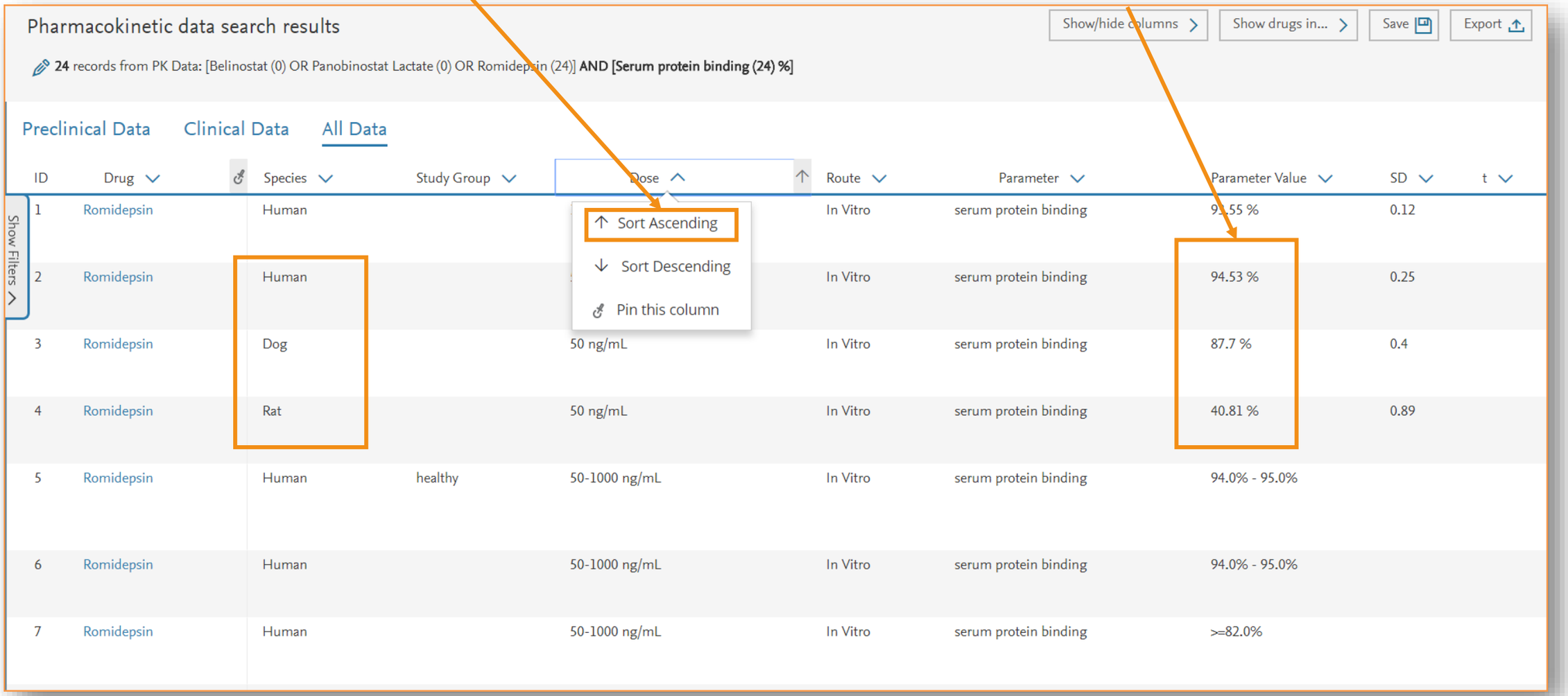


- 结果集中，快速的筛选出血清蛋白结合的临床前和临床数据

Pharmacokinetic

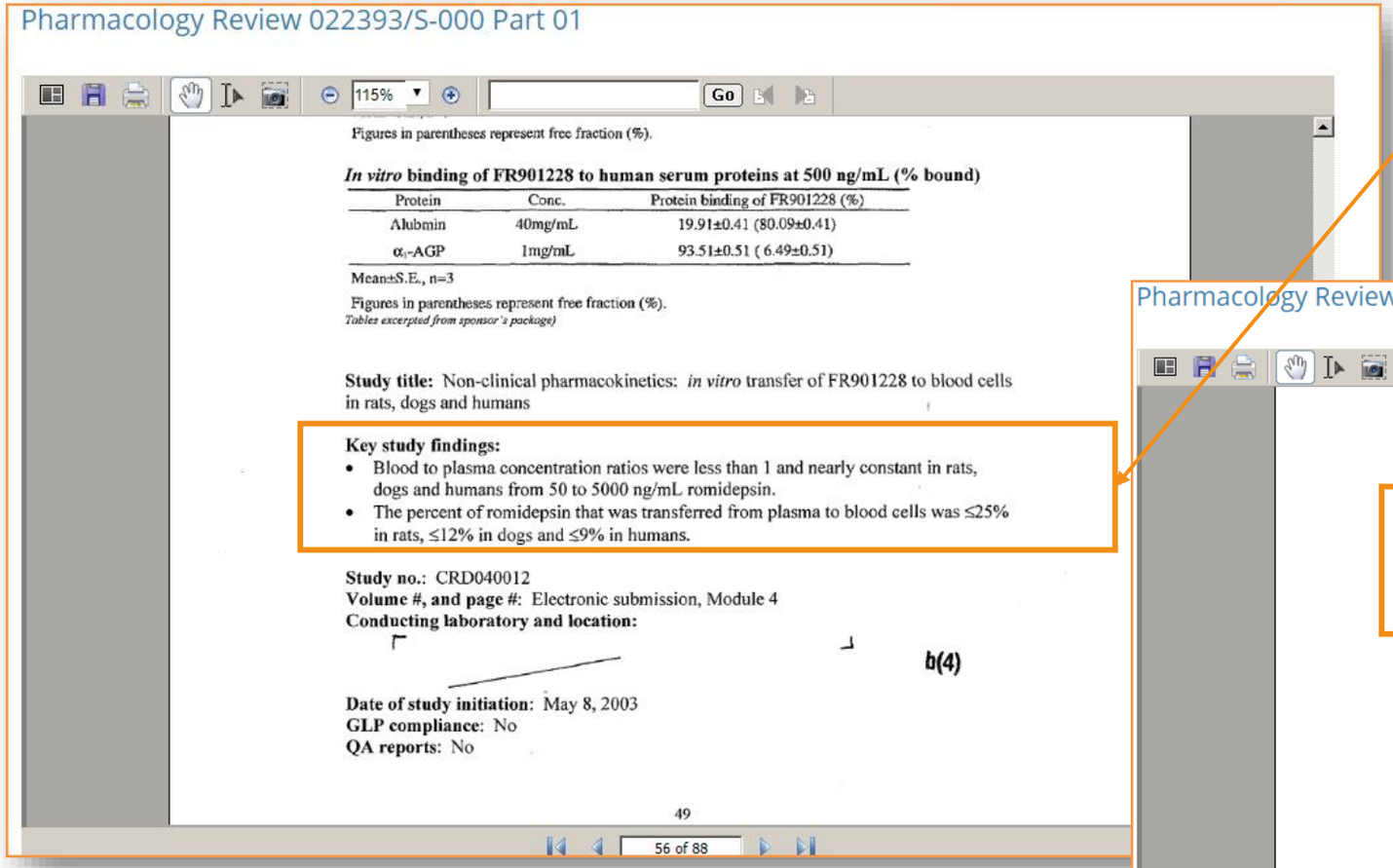
通过‘给药剂量’排序

- 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**

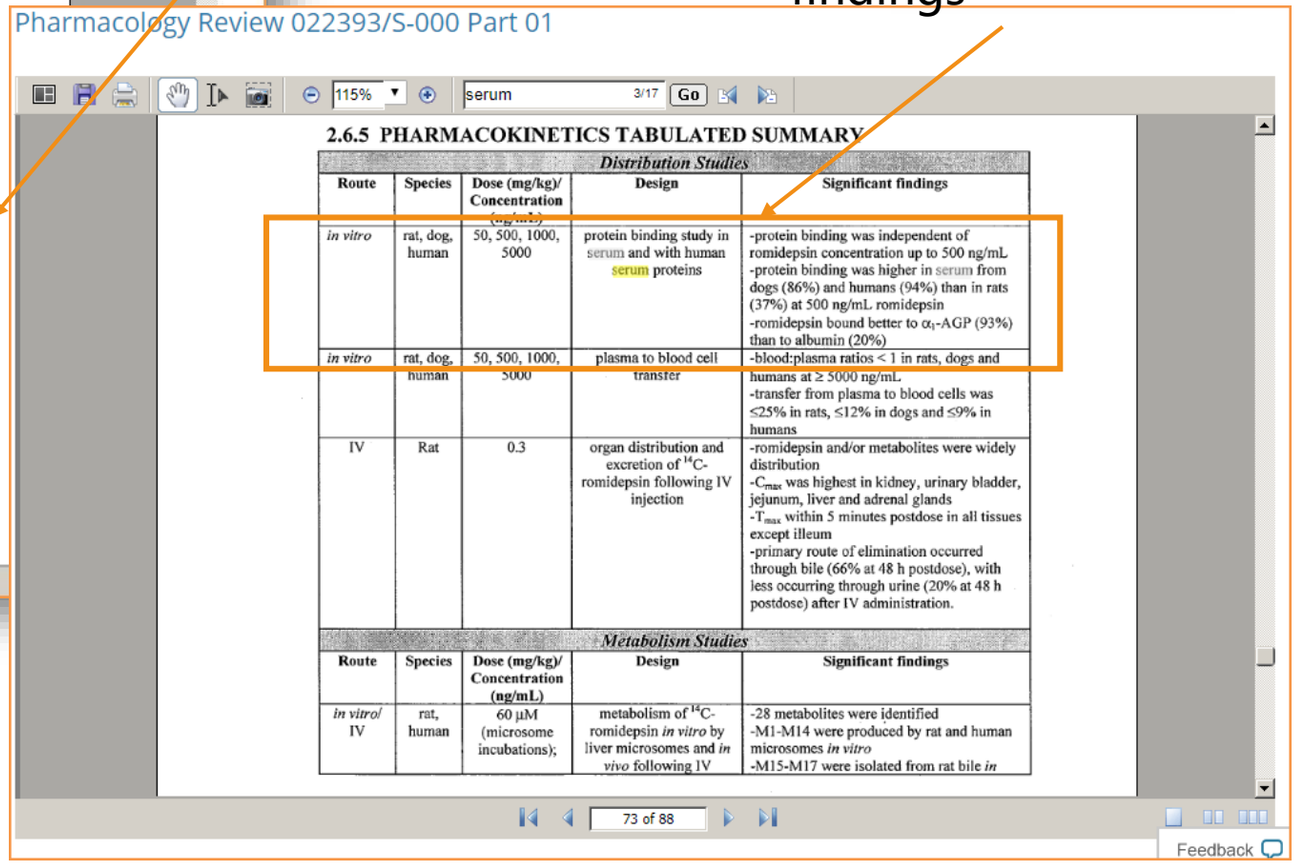


ID	Drug	Species	Study Group	Dose	Route	Parameter	Parameter Value	SD	t
1	Romidepsin	Human			In Vitro	serum protein binding	91.55 %	0.12	
2	Romidepsin	Human			In Vitro	serum protein binding	94.53 %	0.25	
3	Romidepsin	Dog		50 ng/mL	In Vitro	serum protein binding	87.7 %	0.4	
4	Romidepsin	Rat		50 ng/mL	In 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



- 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'



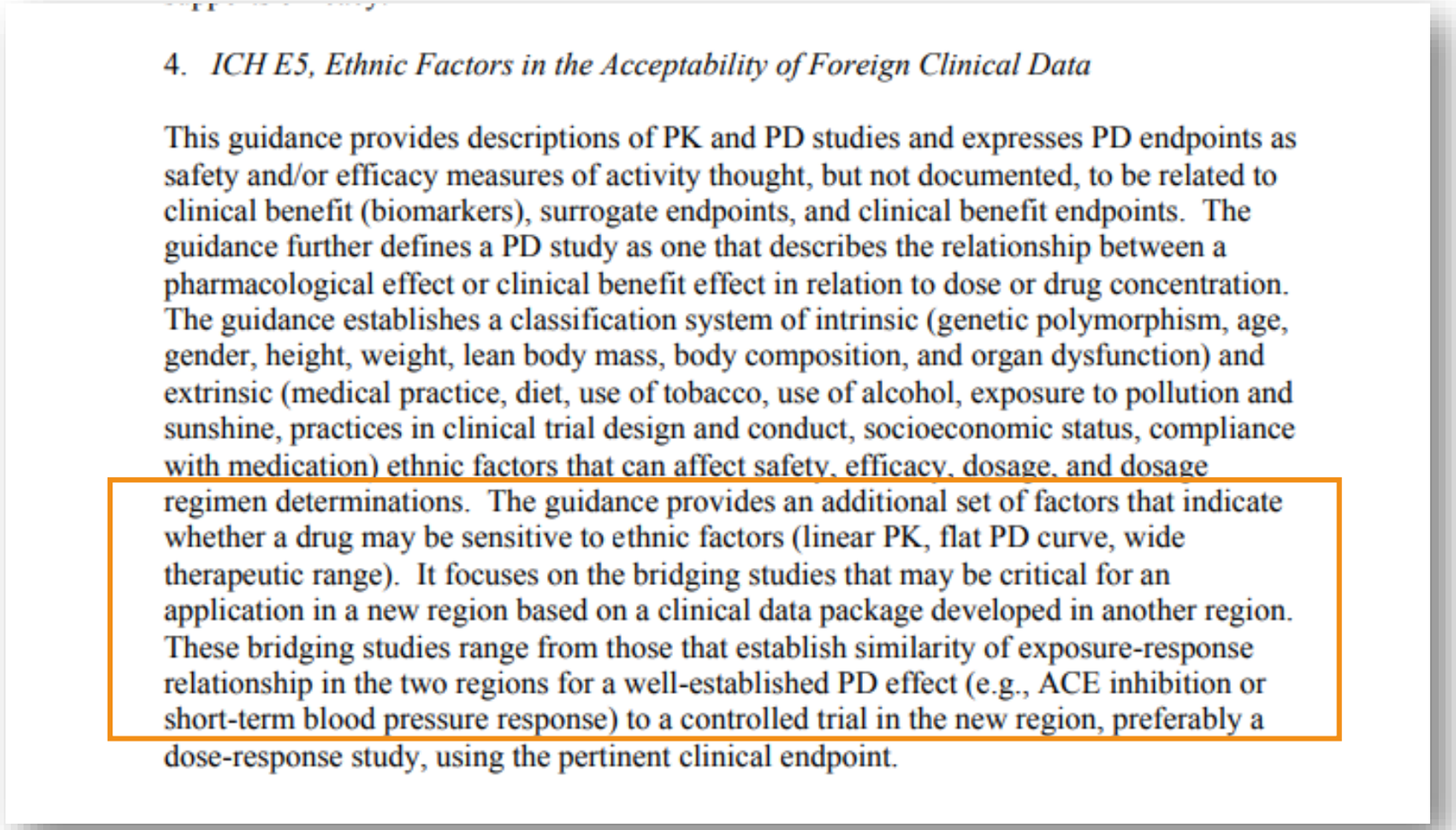
药代信息检索：种族对与同类型药物给药剂量的影响

ELSEVIER

Empowering Knowledge

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.

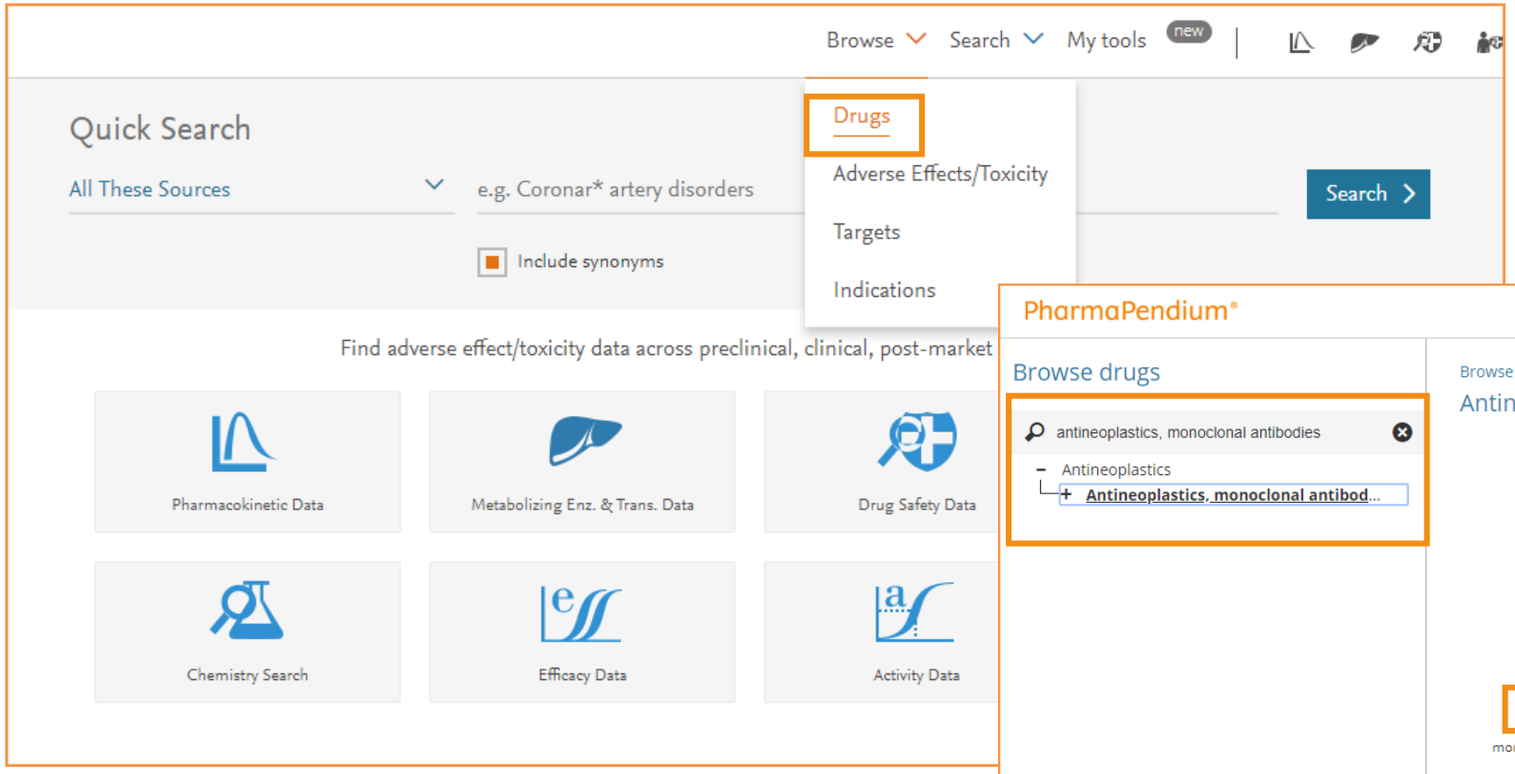
- 在FDA的知道文件当中注明，种族因素是一个影响药效和安全的重要因素，因此在设计临床实验，以及IND, NDA申请的时候需要考虑这些因素对在研药物的影响，**那么快速高效的收集相关信息，有助于决策**

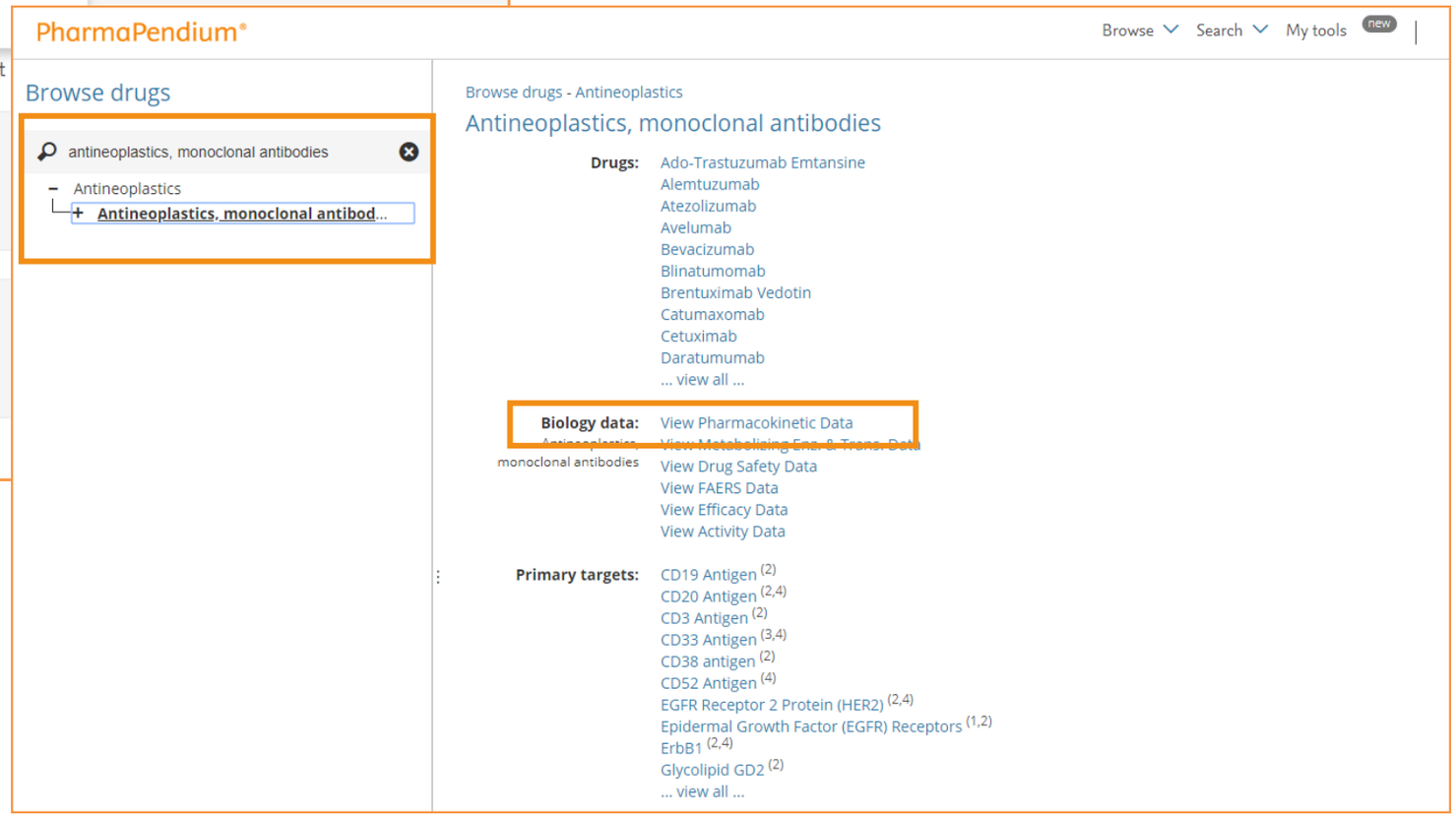
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf

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

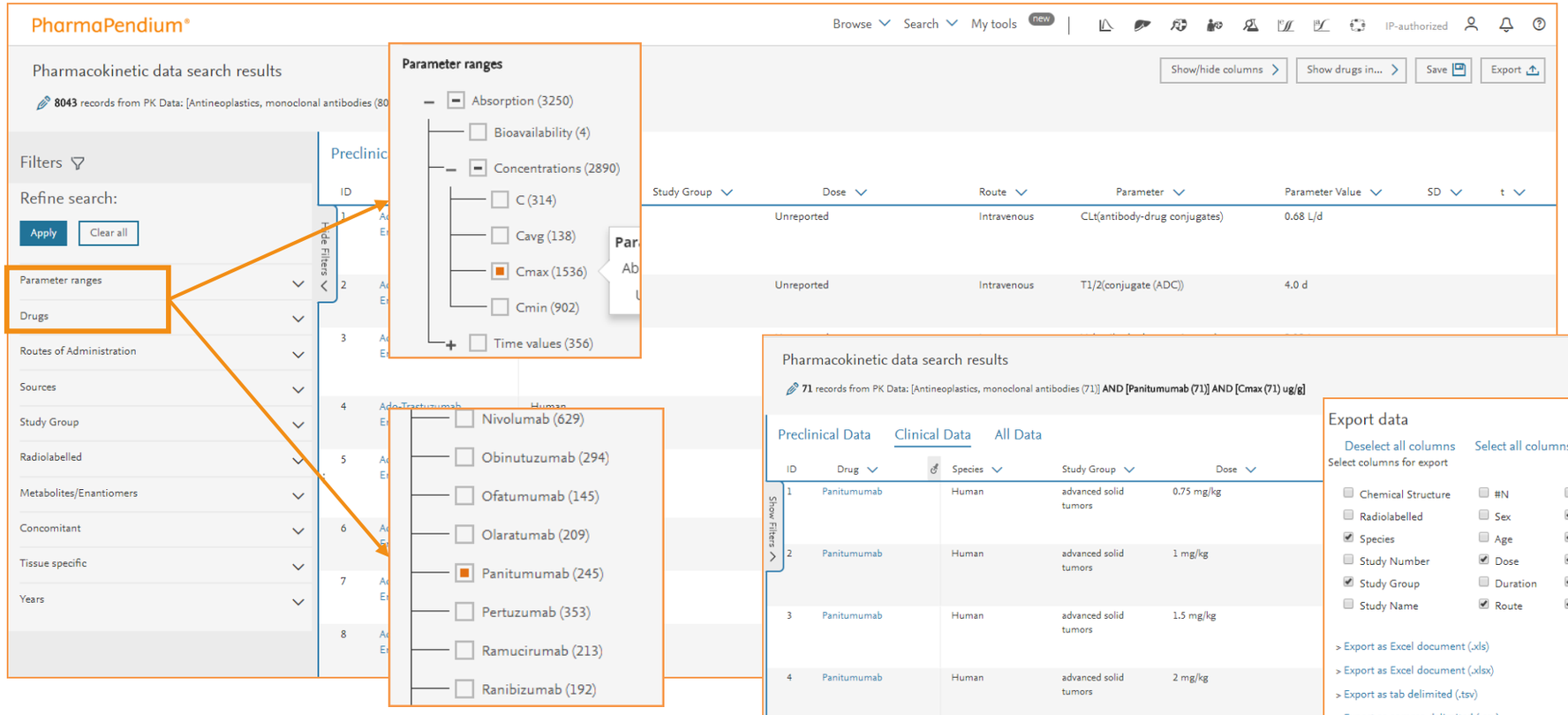


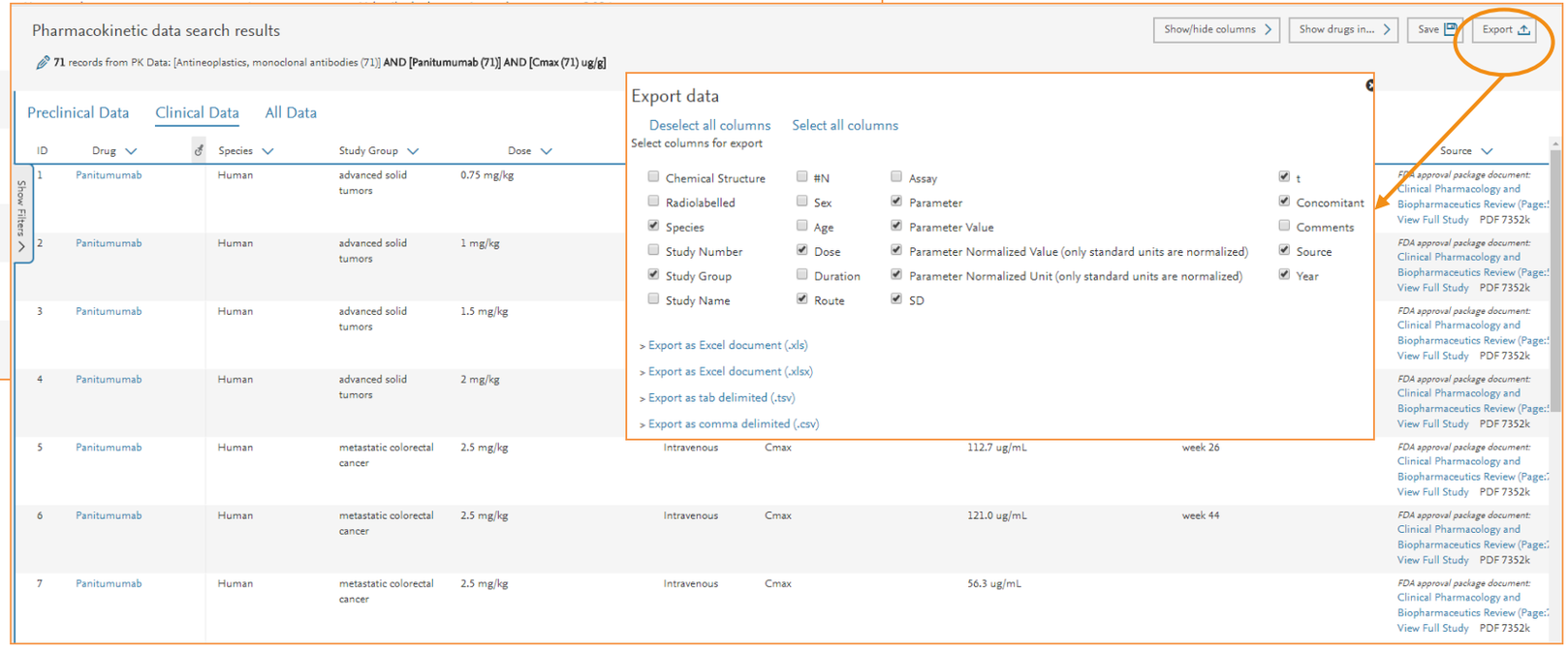


- 通过PP能够快速通过 ‘某一类药物’ 搜集到approval文件中的PK数据

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





- 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---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

Export date: 02-07-2018
Pharmacokinetic Data Search Results For: Drugs: [Antineoplastics, monoclonal antibodies (71)] AND [Panitumumab (71)] AND Parameters: [Cmax (71) ug/g]
Total results: 71
Sort order: Dose (Ascending); Drug (Ascending);

Drug	Species	Study Group	Dose	Route	Parameter	Value	Units	Parameter Normalized Value (only standard units are normalized)	Parameter
Panitumumab	Human	advanced solid tumors	0.75 mg/kg	Intravenous	Cmax	14 (9 to 20)	ug/mL	14 (9 to 20)	ug/mL
Panitumumab	Human	advanced solid tumors	1 mg/kg	Intravenous	Cmax	28 (24 to 31)	ug/mL	28 (24 to 31)	ug/mL
Panitumumab	Human	advanced solid tumors	1.5 mg/kg	Intravenous	Cmax	34 (26 to 40)	ug/mL	34 (26 to 40)	ug/mL
Panitumumab	Human	advanced solid tumors	2 mg/kg	Intravenous	Cmax	50 (40 to 53)	ug/mL	50 (40 to 53)	ug/mL
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	112.7	ug/mL	112.7 (112.7 to 112.7)	ug/mL
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	121	ug/mL	121 (121 to 121)	ug/mL
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous	Cmax	56.3	ug/mL	56.3 (56.3 to 56.3)	ug/mL
Panitumumab	Human	advanced solid tumors	2.5 mg/kg	Intravenous	Cmax	63 (50 to 86)	ug/mL	63 (50 to 86)	ug/mL
Panitumumab	Human	advanced solid tumors	2.5 mg/kg	Intravenous	Cmax	64	ug/mL	64 (64 to 64)	ug/mL
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg						
Panitumumab	Human	Japanese with advanced solid tumors	2.5 mg/kg						
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg						
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg						
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg						
Panitumumab	Human	Japanese with advanced solid tumors	2.5 mg/kg						
Panitumumab	Human		2.5 mg/kg						
Panitumumab	Human	renal carcinoma	2.5 mg/kg/wk						
Panitumumab	Human	advanced solid tumors	3.5 mg/kg						
Panitumumab	Human	advanced solid tumors	5 mg/kg						
Panitumumab	Human	colorectal cancer, various other solid tumour	6 mg/kg						
Panitumumab	Human	metastatic colorectal cancer	6 mg/kg						
Panitumumab	Human	advanced solid tumors	6 mg/kg						
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg						
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg						
Panitumumab	Human		6 mg/kg						
Panitumumab	Human		6 mg/kg						
Panitumumab	Human	advanced solid tumors	6 mg/kg						
Panitumumab	Human	advanced solid tumors	6 mg/kg						
Panitumumab	Human		6 mg/kg						
Panitumumab	Human	Japanese with advanced solid tumors	6 mg/kg						
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg						
Panitumumab	Human		6 mg/kg						
Panitumumab	Human		6 mg/kg						

	Parameter Normalized Unit (only standard units are normalized)	SD	t	Concomitant	Source	Source Link	Year
7	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
8	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
9	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
10	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
11	ug/mL		week 26		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
12	ug/mL		week 44		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
13	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
14	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
15	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
16	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
17	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
18	ug/mL		week 17		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
19	ug/mL		week 8		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
20	ug/mL		week 35		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
21	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
22	ug/mL	35.0			EMA approval document: Scientific Discussion, page:15 PDF 506k	https://www.pharmapendium.com/#/brov	2007
23	ug/mL	38.0	week 23		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
24	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
25	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
26	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brov	2007
27	ug/mL	24.6	week 23		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
28	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
29	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brov	2007
30	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brov	2007
31	ug/mL	59.0			EMA approval document: ANNEX I, page:16 PDF 477k	https://www.pharmapendium.com/#/brov	
32	ug/mL	59.0			FDA approval package document: Label 125147/S-0067, page:10 PDF 5	https://www.pharmapendium.com/#/brov	2009
33	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
34	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
35	ug/mL	59.0			FDA approval package document: Printed Labeling 125147/S-0000, pag	https://www.pharmapendium.com/#/brov	2006
36	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	303df0e07b424c6?reference=54	
37	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brov	2007
38	ug/mL		after the third dose		FDA approval package document: Administrative documents 125147/S-	https://www.pharmapendium.com/#/brov	2006
39	ug/mL	59.0			FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
40	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brov	
41	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brov	2007
42	ug/mL		after the third dose		FDA approval package document: Administrative documents 125147/S-	https://www.pharmapendium.com/#/brov	2006
43	ug/mL	59.0			FDA approval package document: Label 125147/S-0000, page:2 PDF 13	https://www.pharmapendium.com/#/brov	2006

Pharmacokinetic Data

➤ 导出表格，**规整易读，便于统计管理数据**，当需要查看原文时，可以根据表格中的原文连接，直接查看原文

Pharmacokinetic---原始文献查看

FDA Approval Package - Panitumumab > Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review 125147/S-0000

115% japanese 13/37 Go

of arithmetic mean values expressed as a percentage
[b]Study 20030138 for the 2.5 mg/kg group and Study 20030251 for the 6 mg/kg group.
Source: \\documentum\Docbases\usddmst\R&D Candidates\Development\AMG 954 - ABX-EGF\Preclinical Non-Study Specific\PKDM\Submission\BLA\Clinical\Supporting data\winonlinux 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

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

115% japanese 12/37 Go

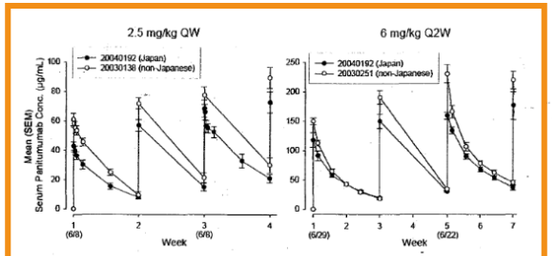


FIGURE 16: Comparison of Mean (SE) PK Profiles between Non-Japanese (Studies 20030138 and 20030251) and Japanese Subjects (Study 20040192)

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.

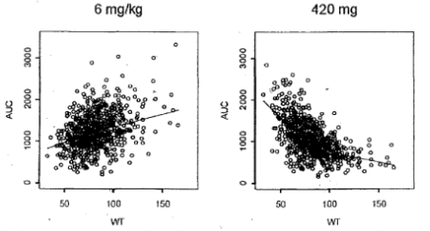


FIGURE 17: **Relationship between Body Weight and Simulated Steady State Exposure for Panitumumab Administered Once Every 2 Weeks (per sponsor's report # 104311)**

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Feedback

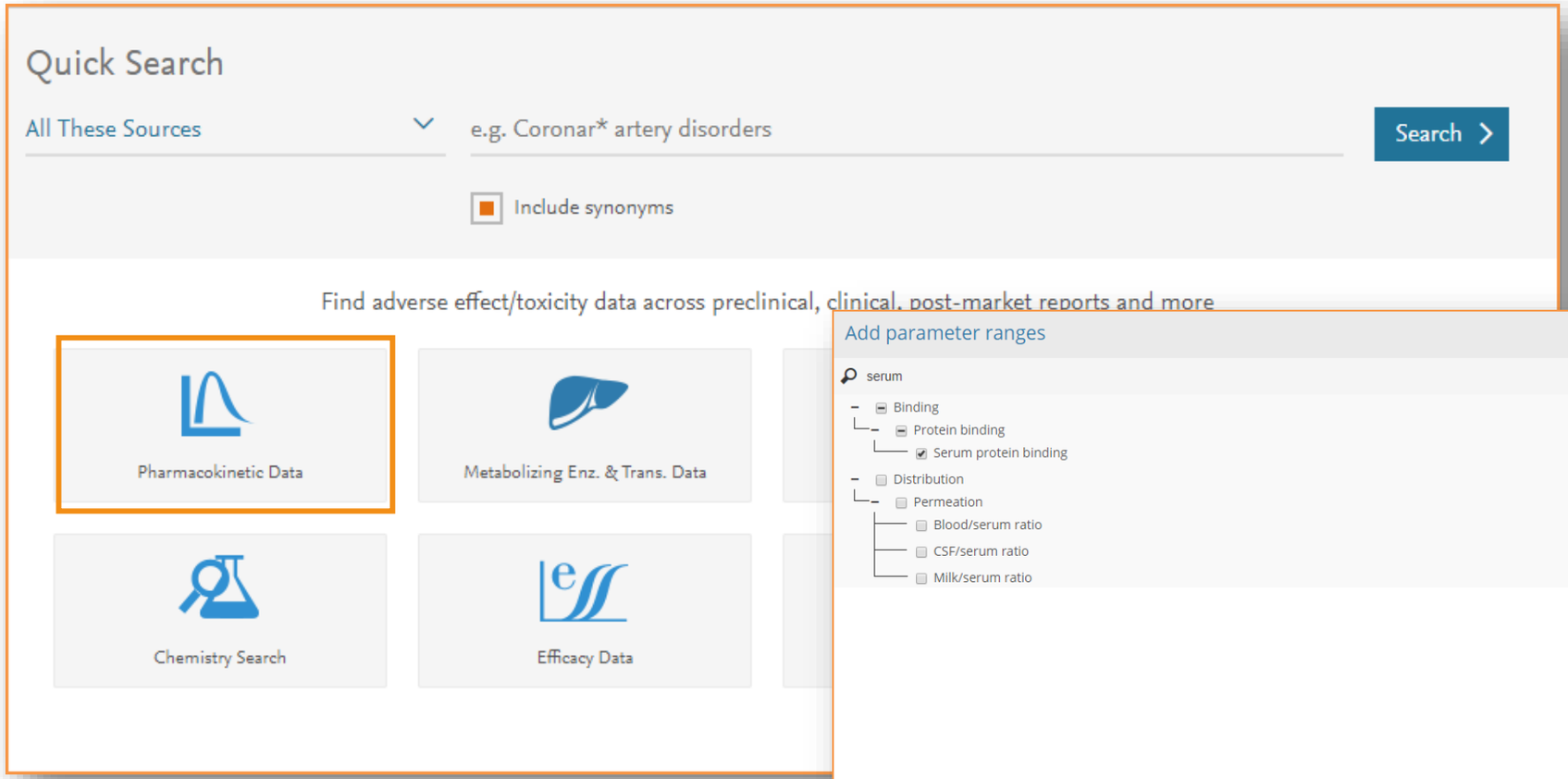
药代动力学：检索血浆结合率<1% 且能抑制CYP3A4药物相关信息

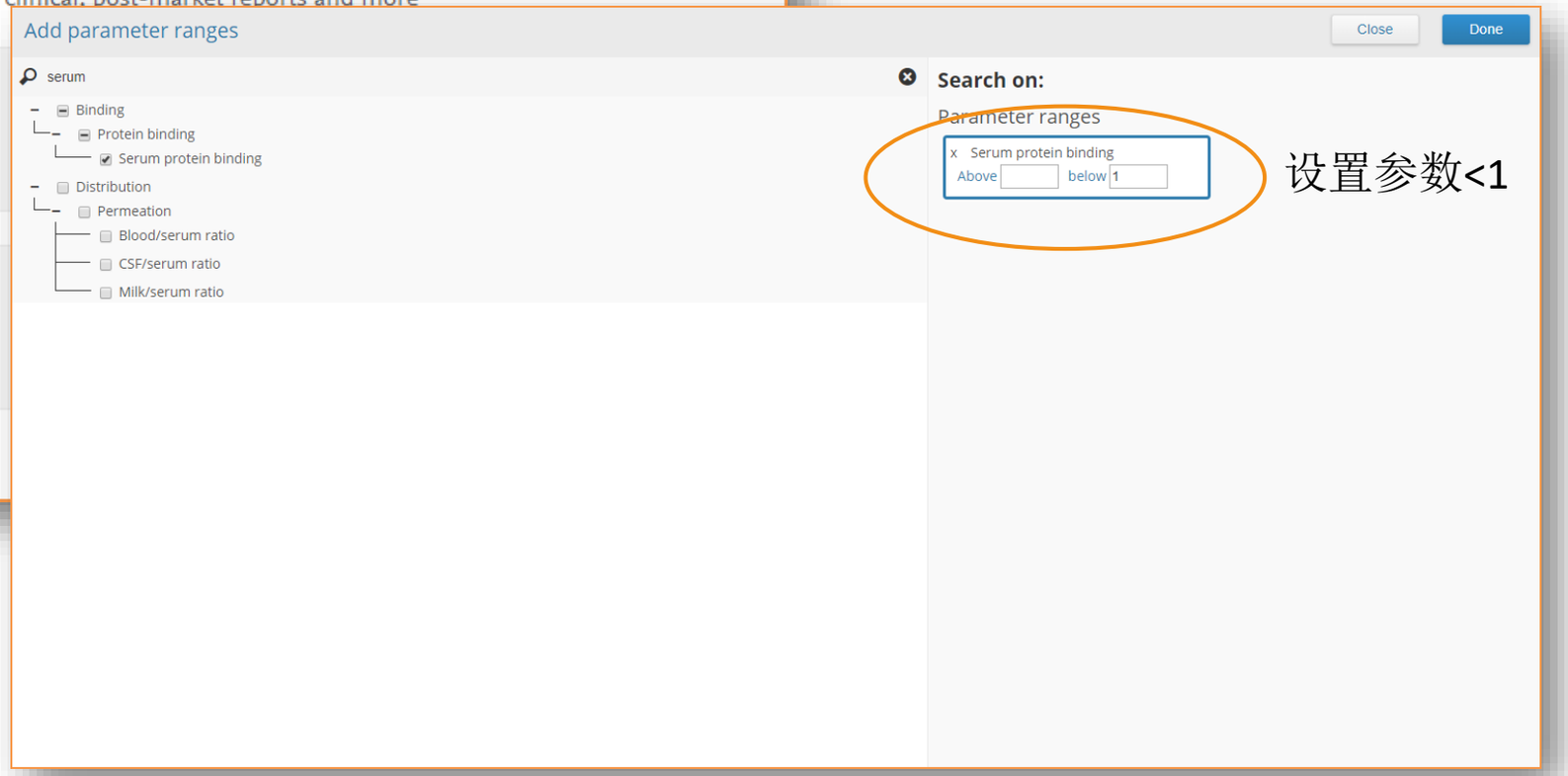
ELSEVIER

Empowering Knowledge

Pharmacokinetic—按条件设置参数

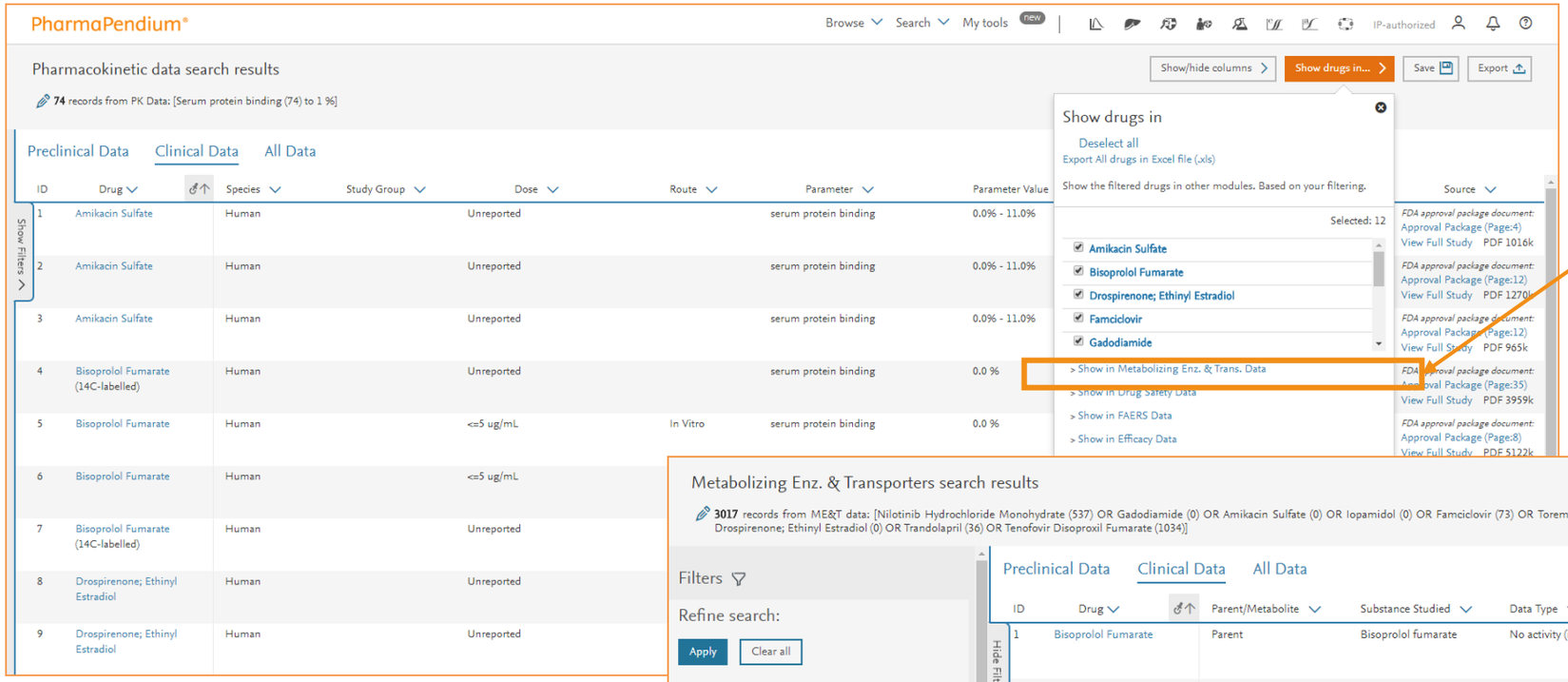
- 检索血清结合率（serum binding）<1%同时又对CYP3A4（肝细胞首过代谢酶）有抑制的药物及其参数信息



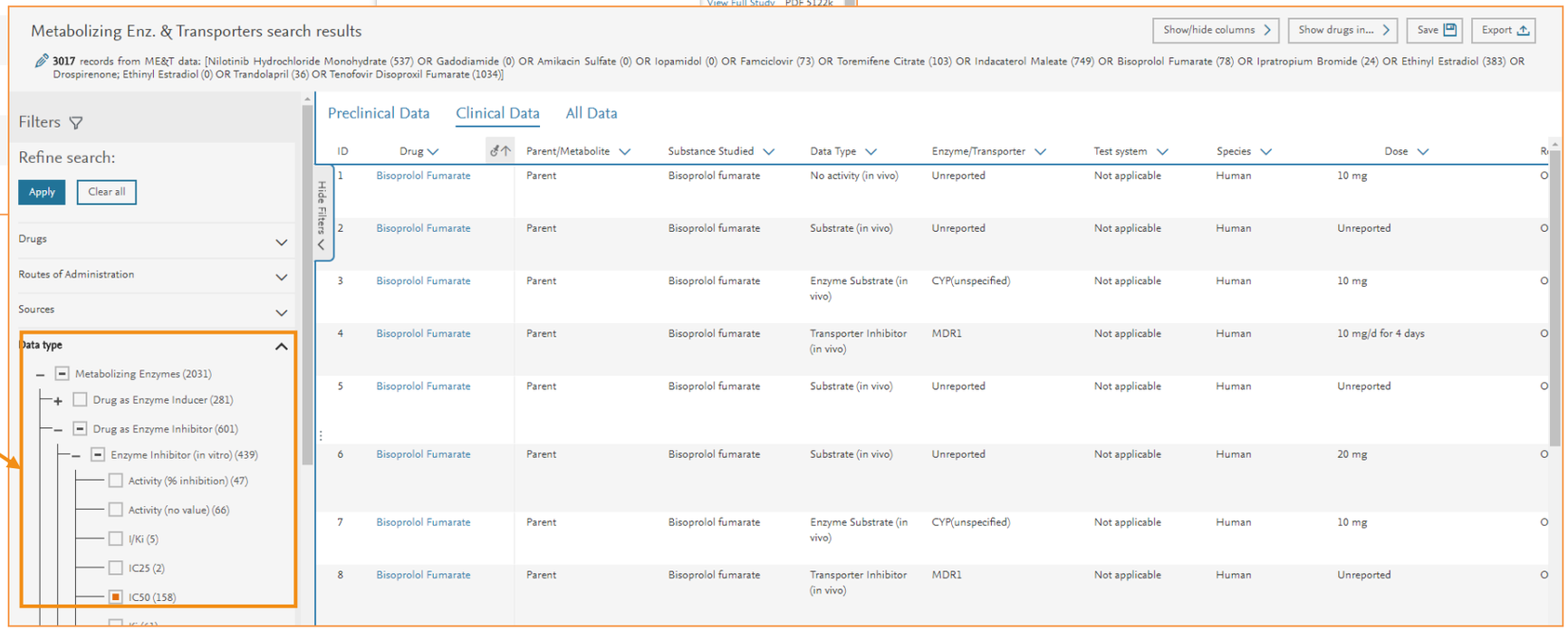


设置参数<1

Pharmacokinetic---快速分类出代谢数据



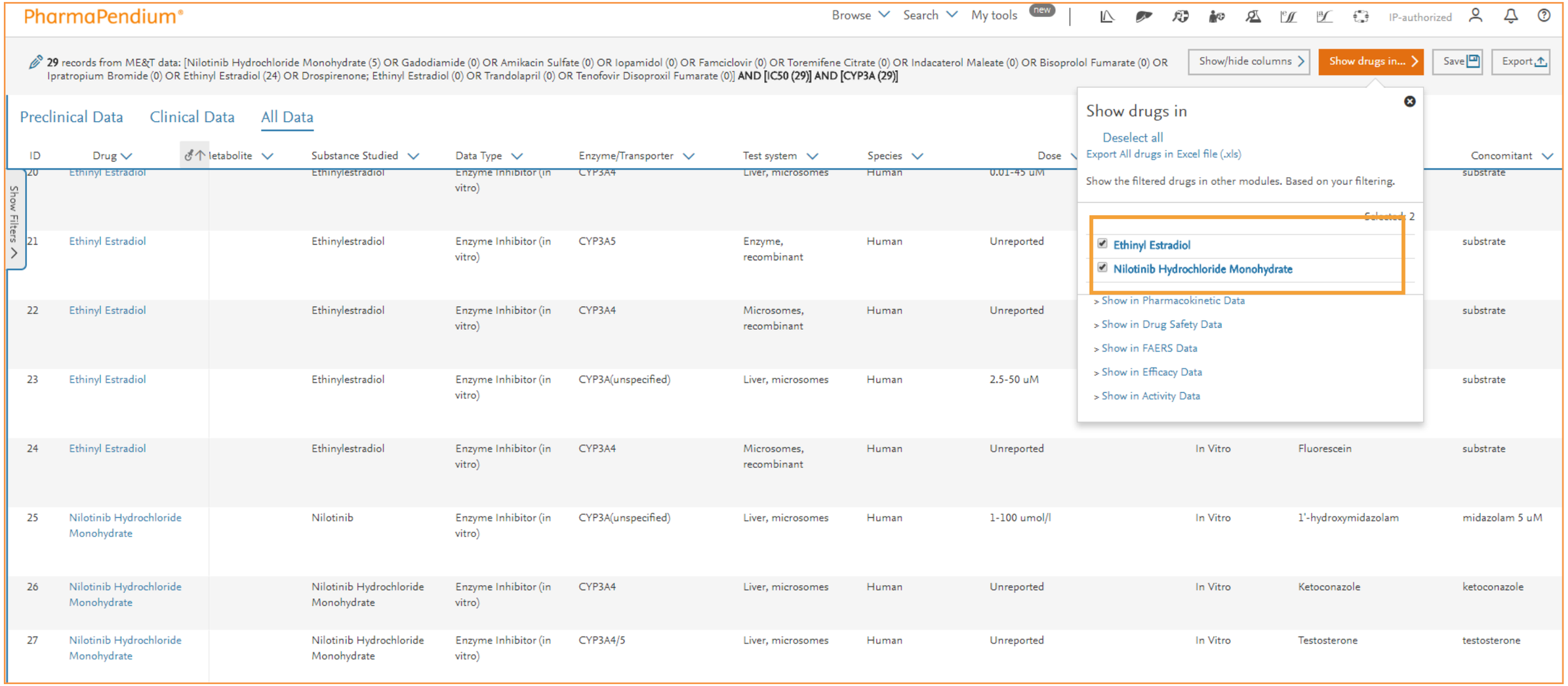
➢ PP提供多种分类的选项交叉筛选：通过metabolizing...把代谢数据筛选出来



➢ 再在结果集中，筛选酶抑制 ‘IC50’

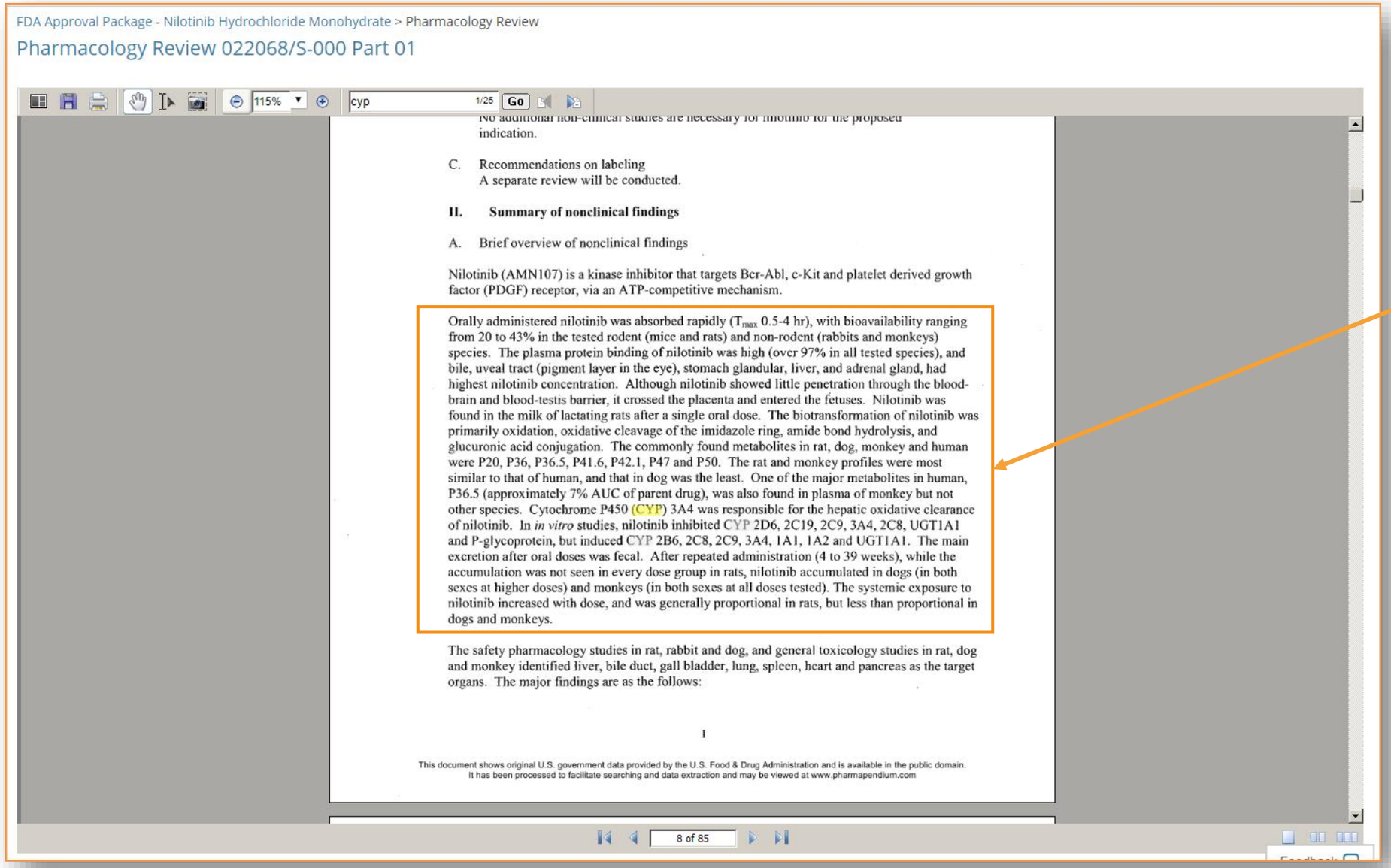
Pharmacokinetic---检索结果

- 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



ID	Drug	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

Pharmacokinetic---原文查看



FDA Approval Package - Nilotinib Hydrochloride Monohydrate > Pharmacology Review

Pharmacology Review 022068/S-000 Part 01

115% cyp 1/25 Go

No additional non-clinical studies are necessary for nilotinib 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

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- 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

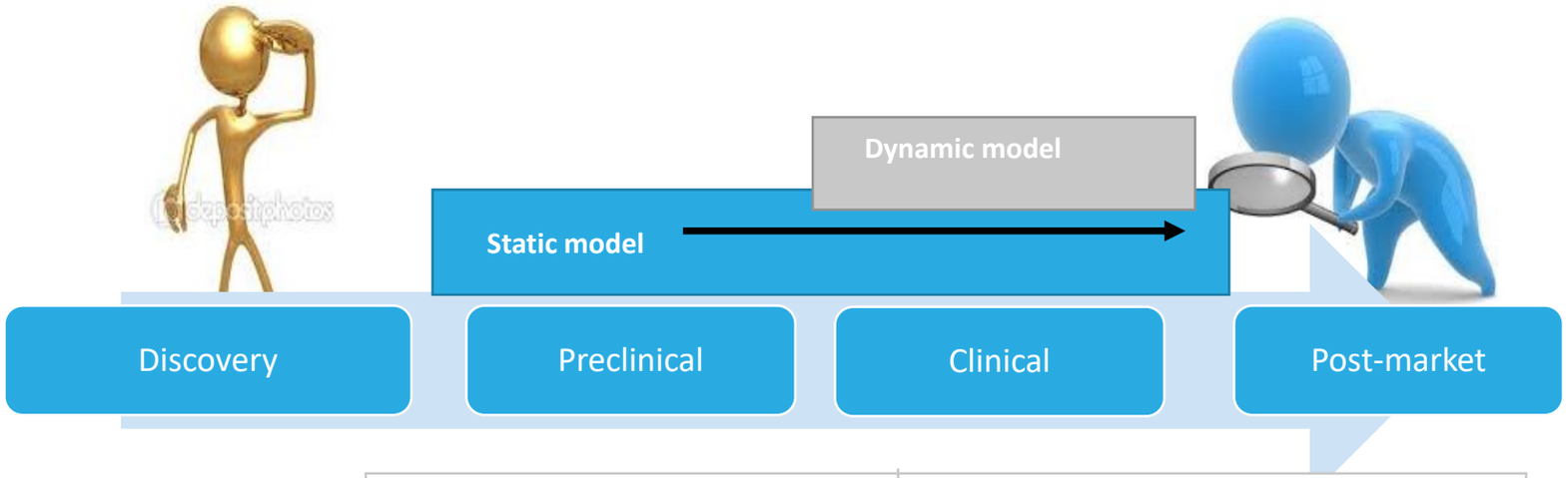
The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

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

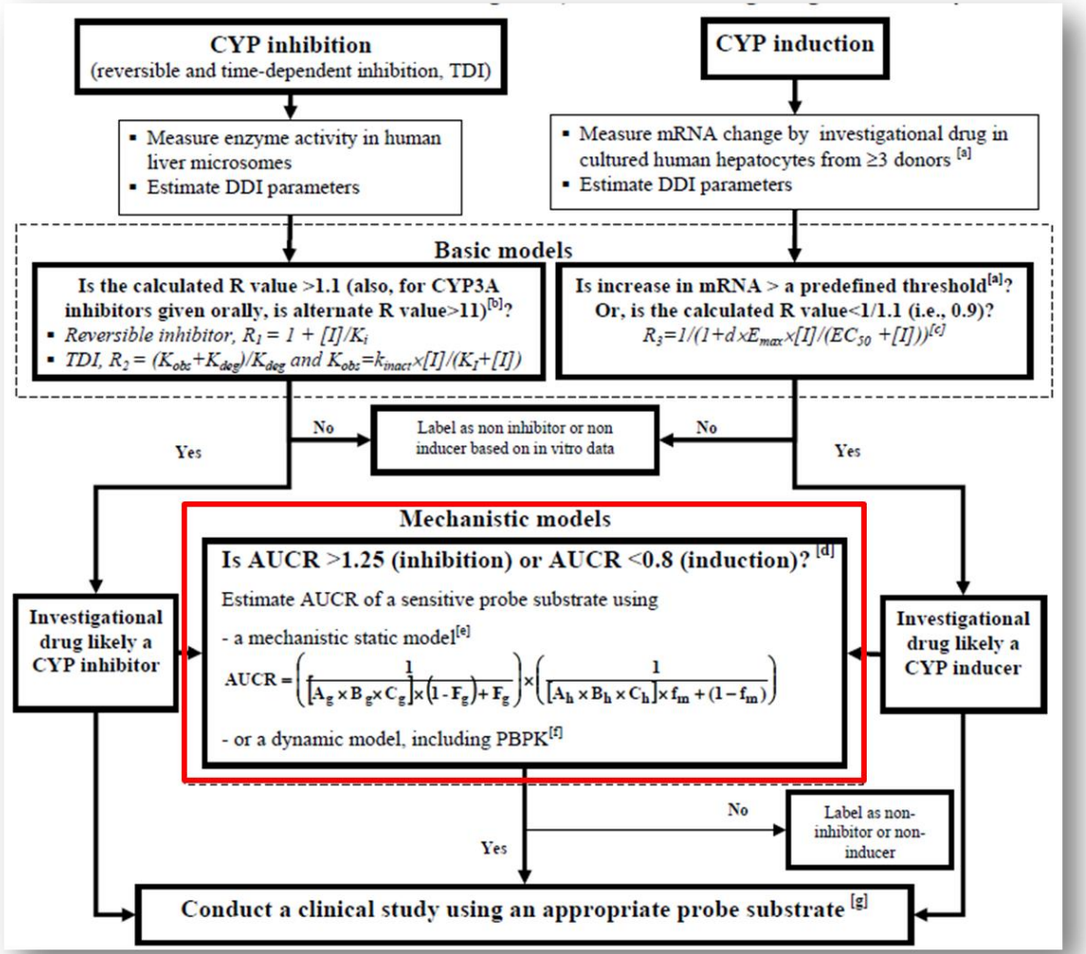
- Information in **Dynamic and Static** models is **complimentary** and used to assesses DDI Risk between specific drugs and to determine what drugs can be used along with a candidate in clinical studies
- Mechanistic Dynamic Modelling (PBPK modelling) requires significant input data and the availability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



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

- Can be used to support exemption from clinical trial assessing DDIR risk
- Can provide evidence for which studies need to be performed

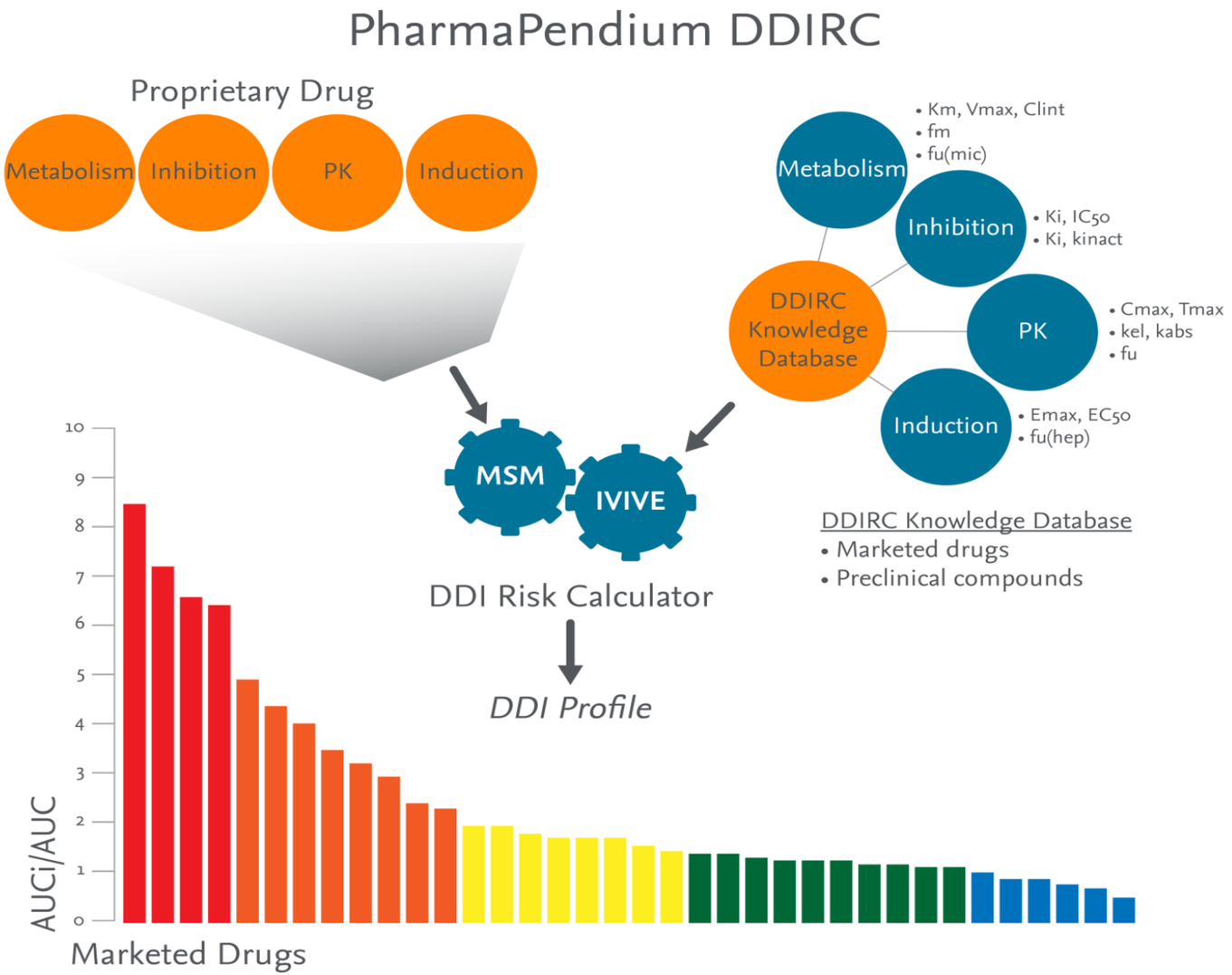
PharmaPendium’ s Drug-Drug Interaction Risk Calculator (DDIRC) 是遵循 2012 and 2017 FDA guidance



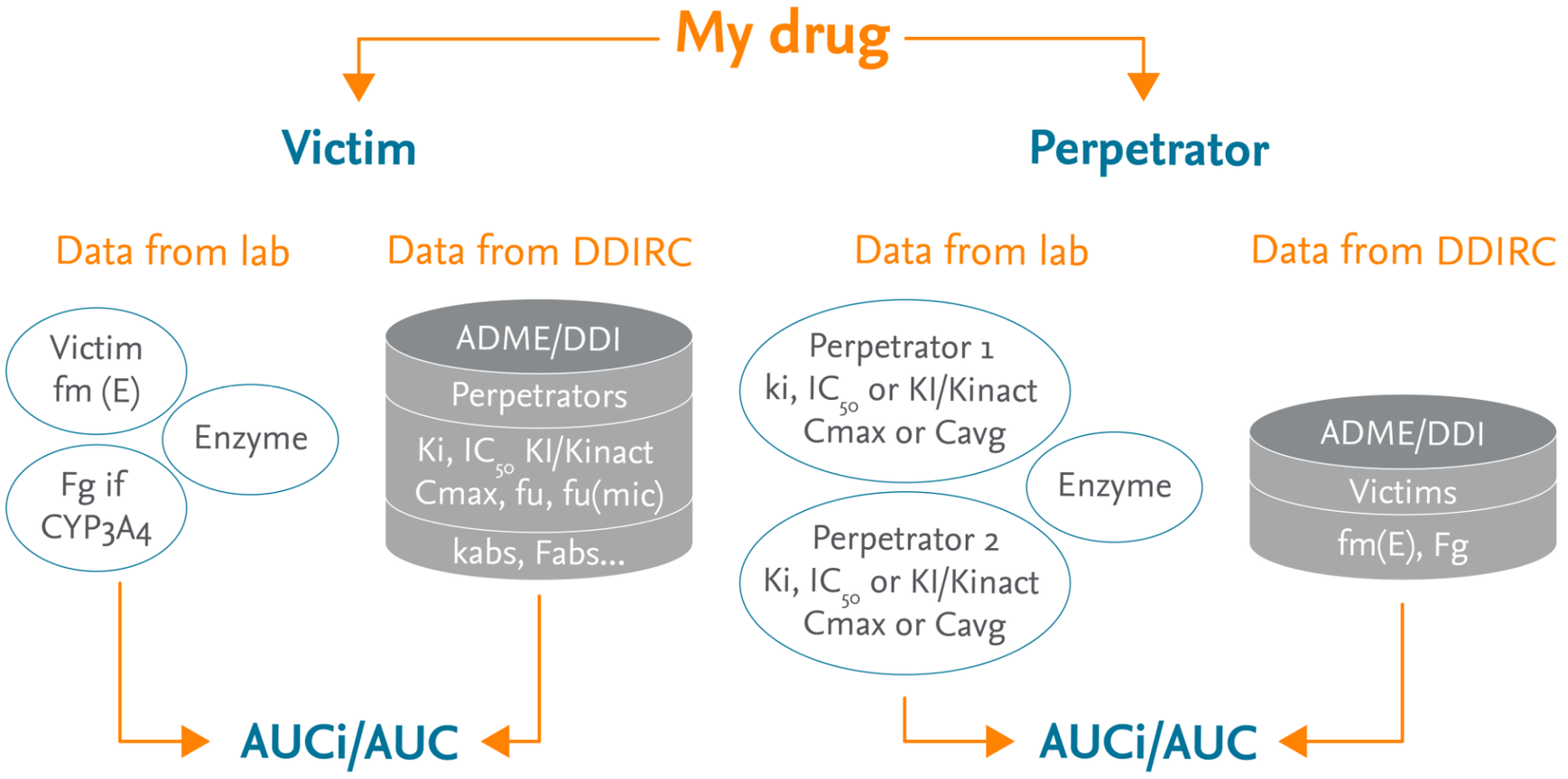
Guidance for Industry Drug Interaction Studies
Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations

“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

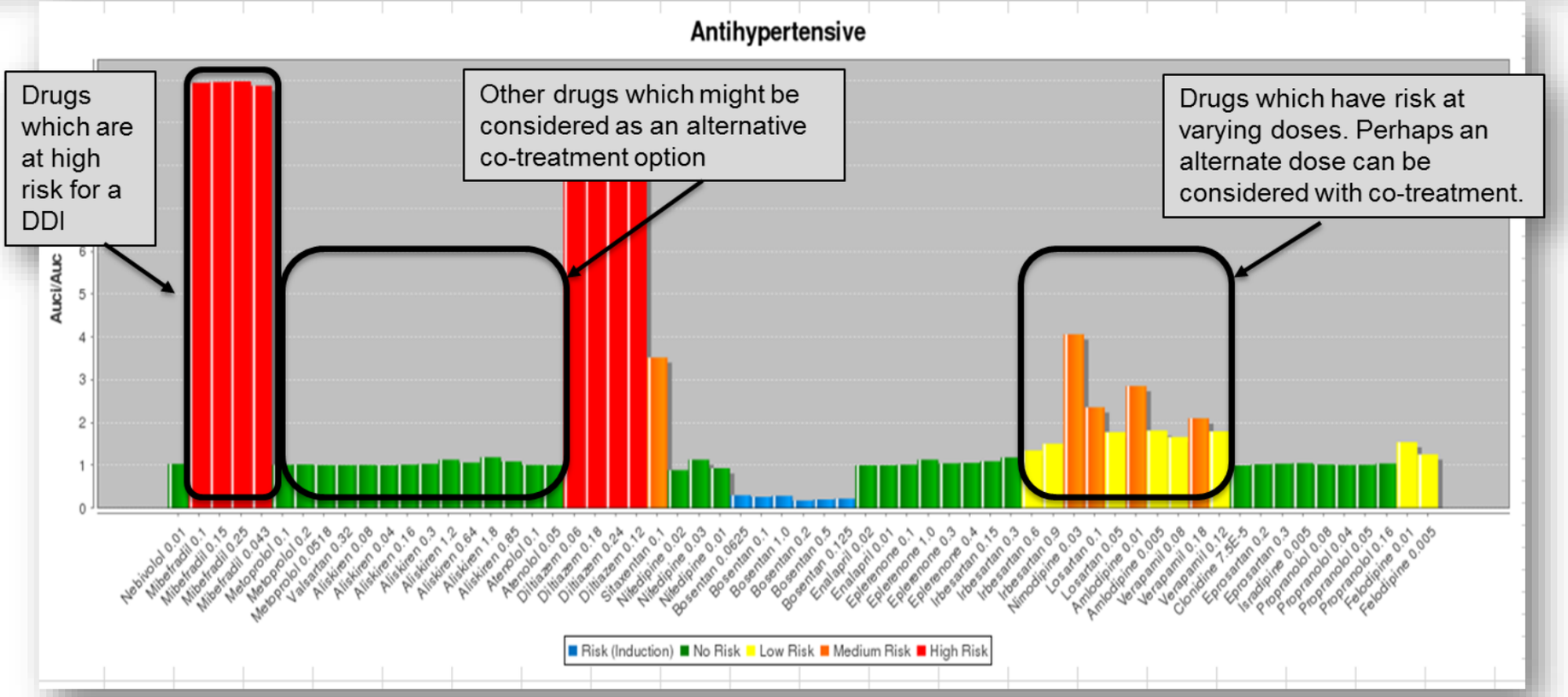


DDIRC 可以自动的运行和操作帮助我们节约了大量的时间

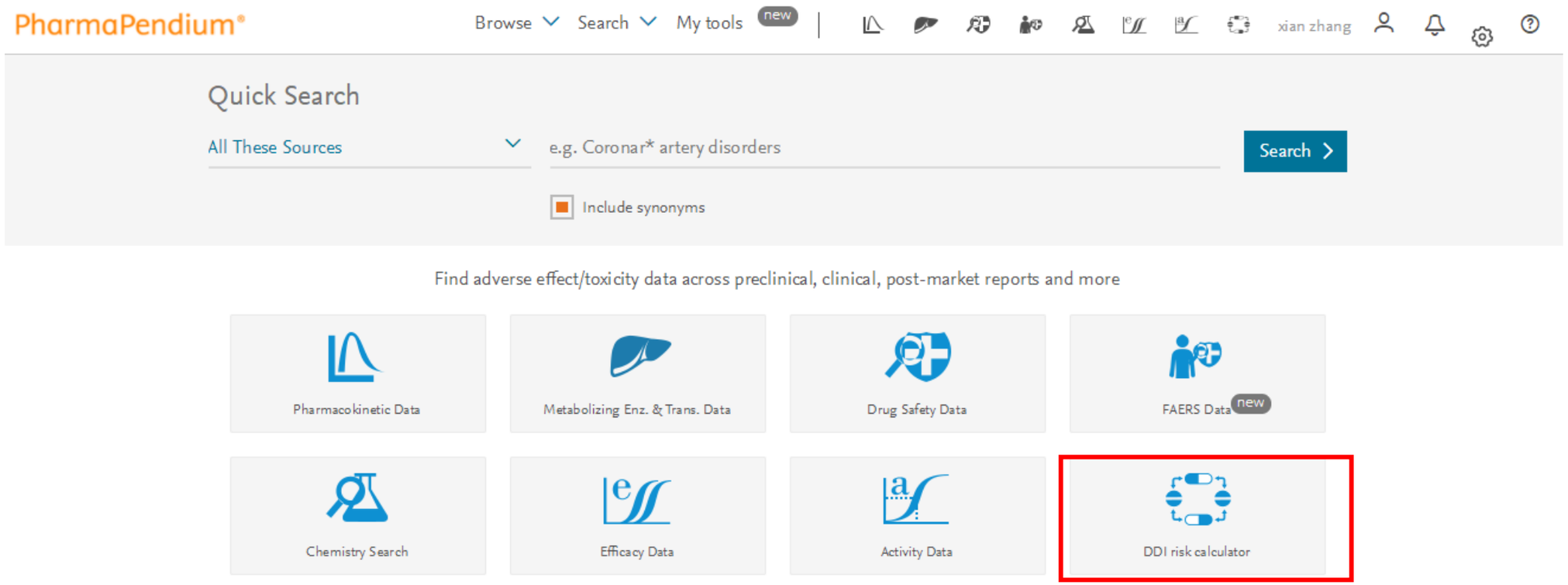


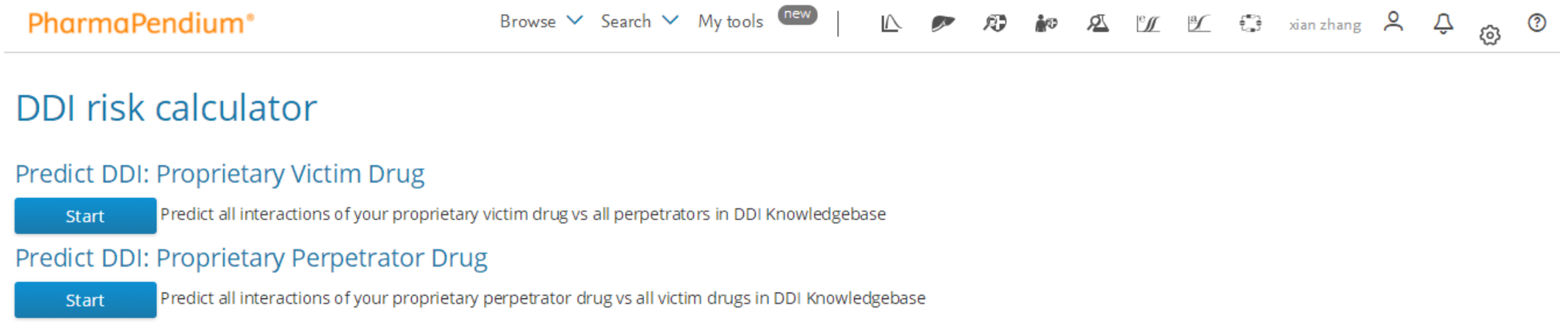
DDIRC 可以快速的提供成百个药物的潜在的相互作用

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?

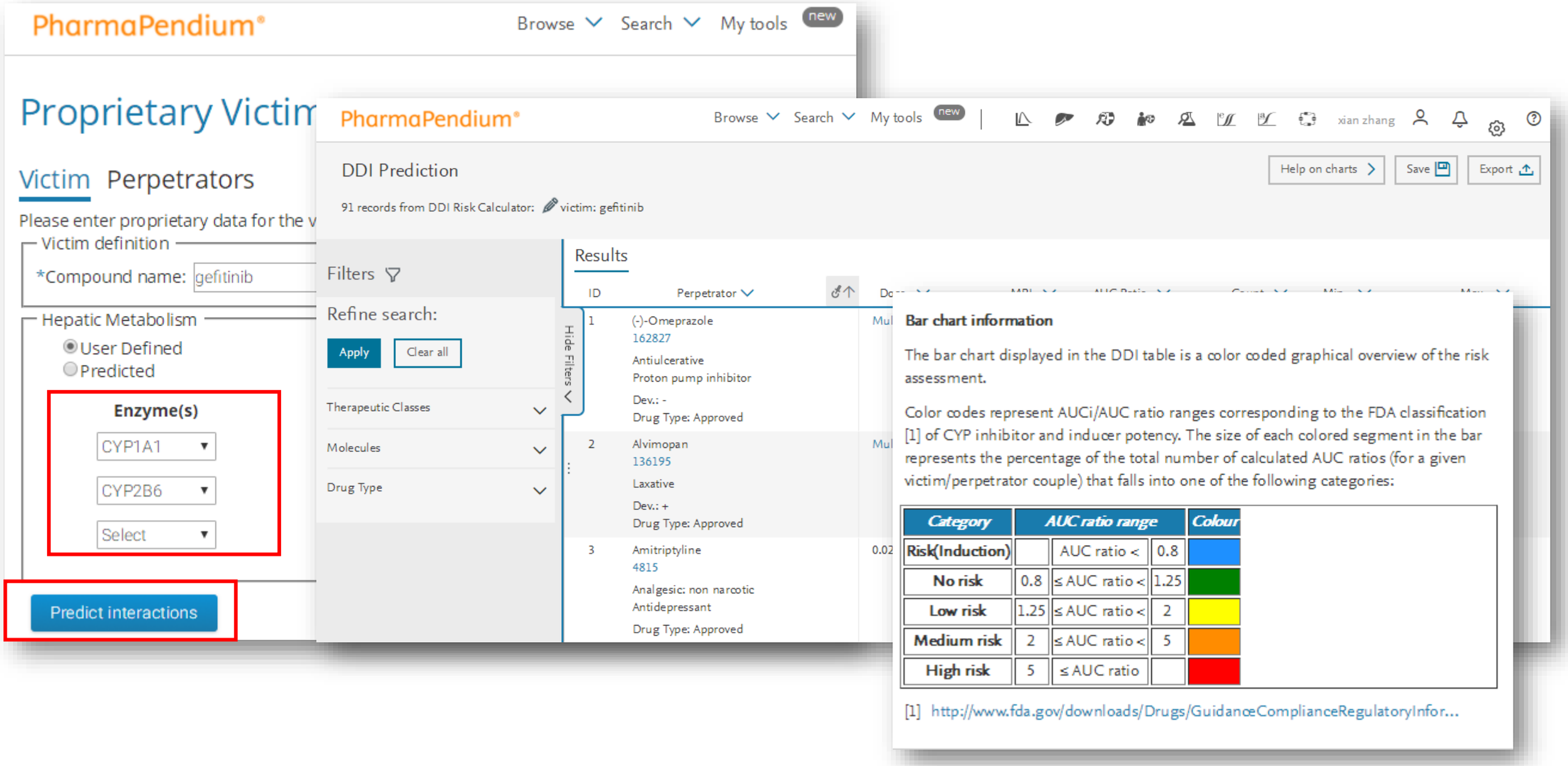


Pharmpendium’ s DDIRC





Pharmpendium’ s DDIRC



感谢聆听，欢迎交流，以及批评指导

THANK YOU!

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