Elsevier Life Science Solution

PharmaPendium介绍以及案例分享

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今天的内容

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

PharmaPendium数据库涵盖的内容

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

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

2.29M+	200K+	9.45M+	673K+
FDA 审评文件	EMA 审评文件	FDA 药物不良反应报告	FDA 咨询委员会会议档案

Extracted Data:	PK Module	MET Module	FDA AERS	Efficacy Module	DDI Risk
4450 种药物的可检索信息	1.6M+ 药代动力学信息	305K+ 药物代谢与转运酶信息	1.66M+ 药物安全信息	2.45M+ 药效信息	115K+ 生物活性信息

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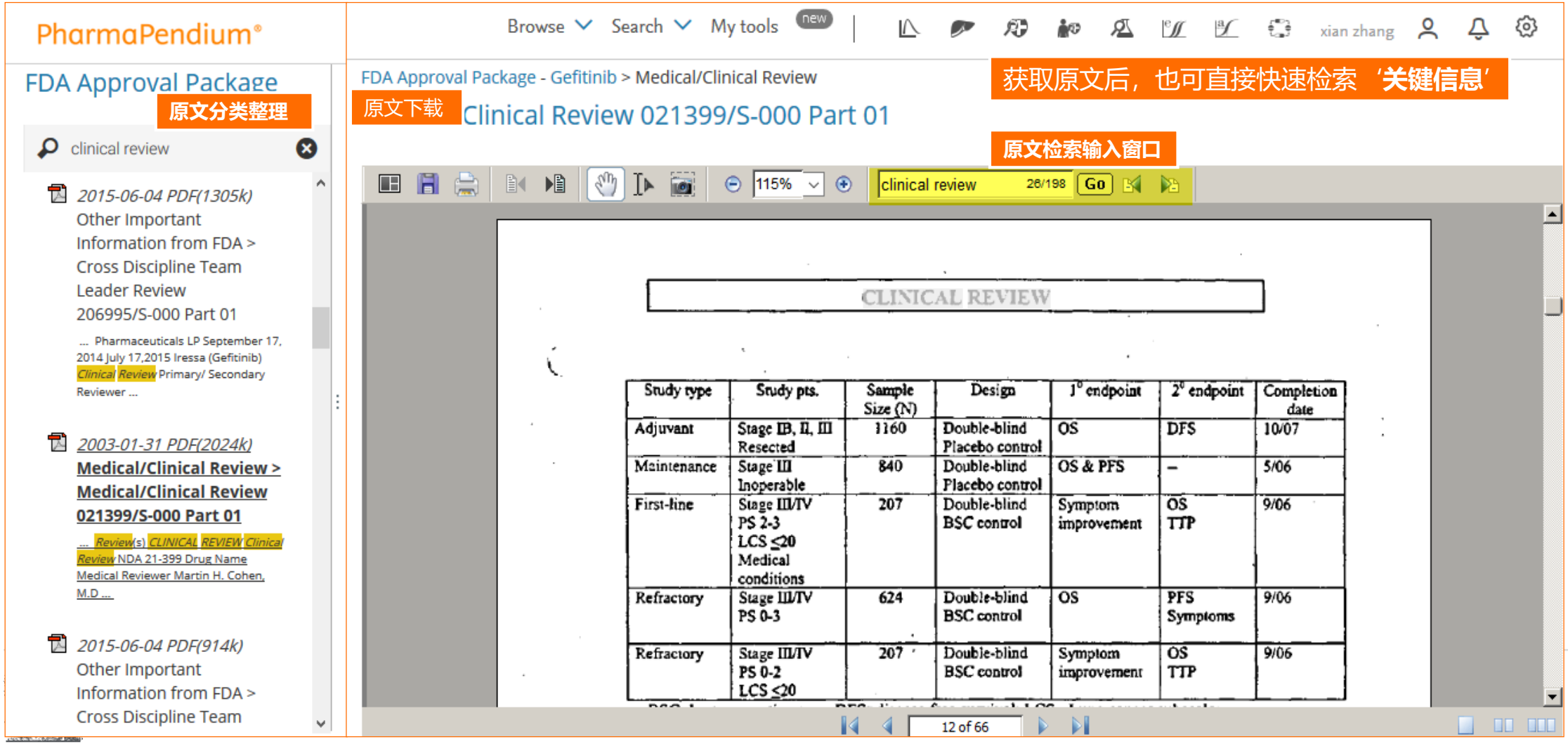
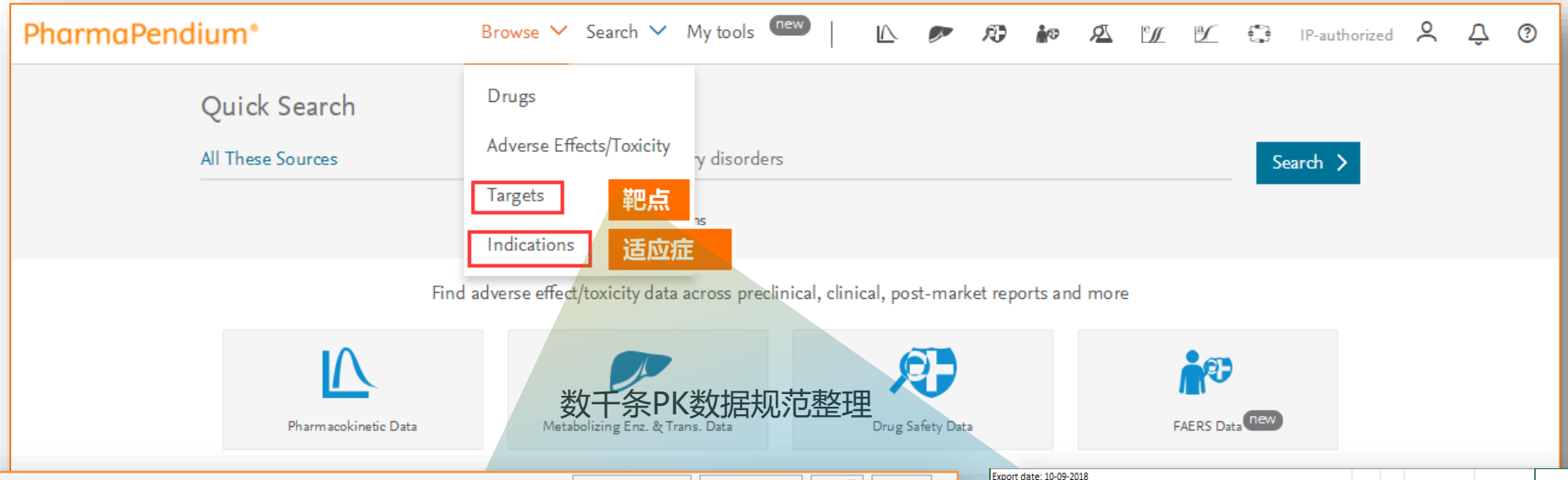
PharmaPendium深度提取FDA,EMA官方文档中的数据

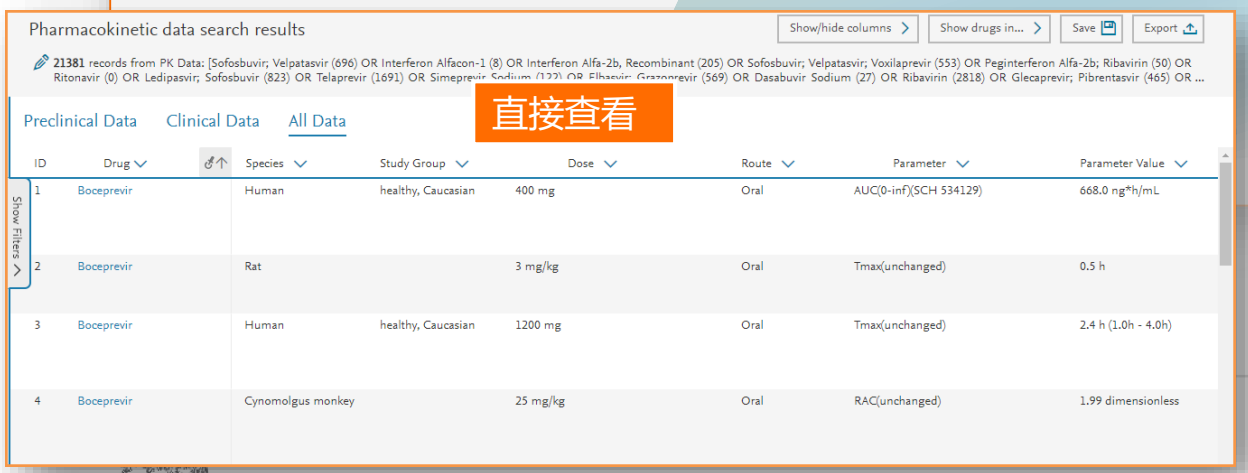


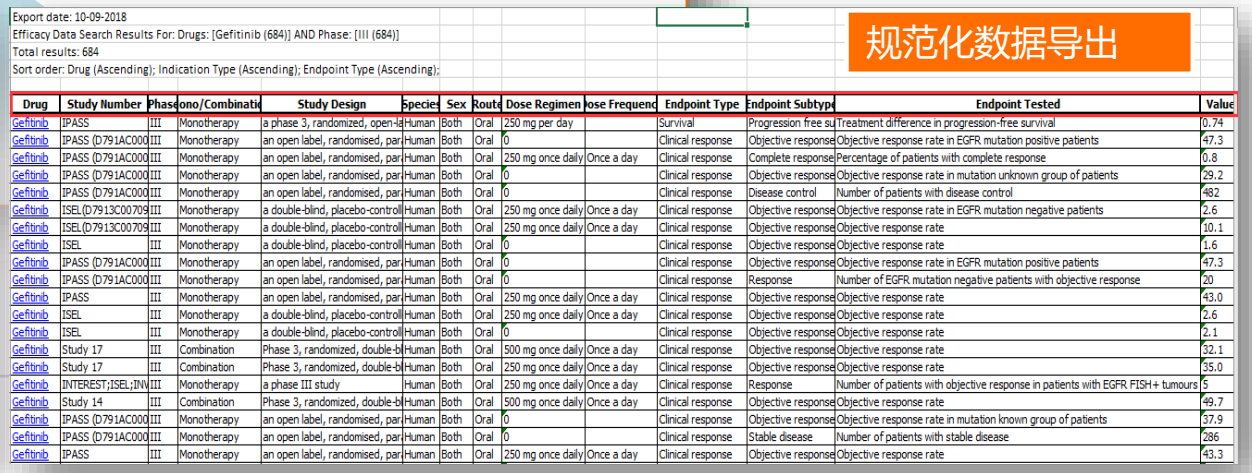
Study type	Study pts.	Sample Size (N)	Design	1° endpoint	2° endpoint	Completion date
Adjuvant	Stage IB, II, III Resected	1160	Double-blind Placebo control	OS	DFS	10/07
Maintenance	Stage III Inoperable	840	Double-blind Placebo control	OS & PFS	–	5/06
First-line	Stage III/IV PS 2-3 LCS ≤20 Medical conditions	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

PharmaPendium深度提取FDA,EMA官方文档中的数据



数千条PK数据规范整理





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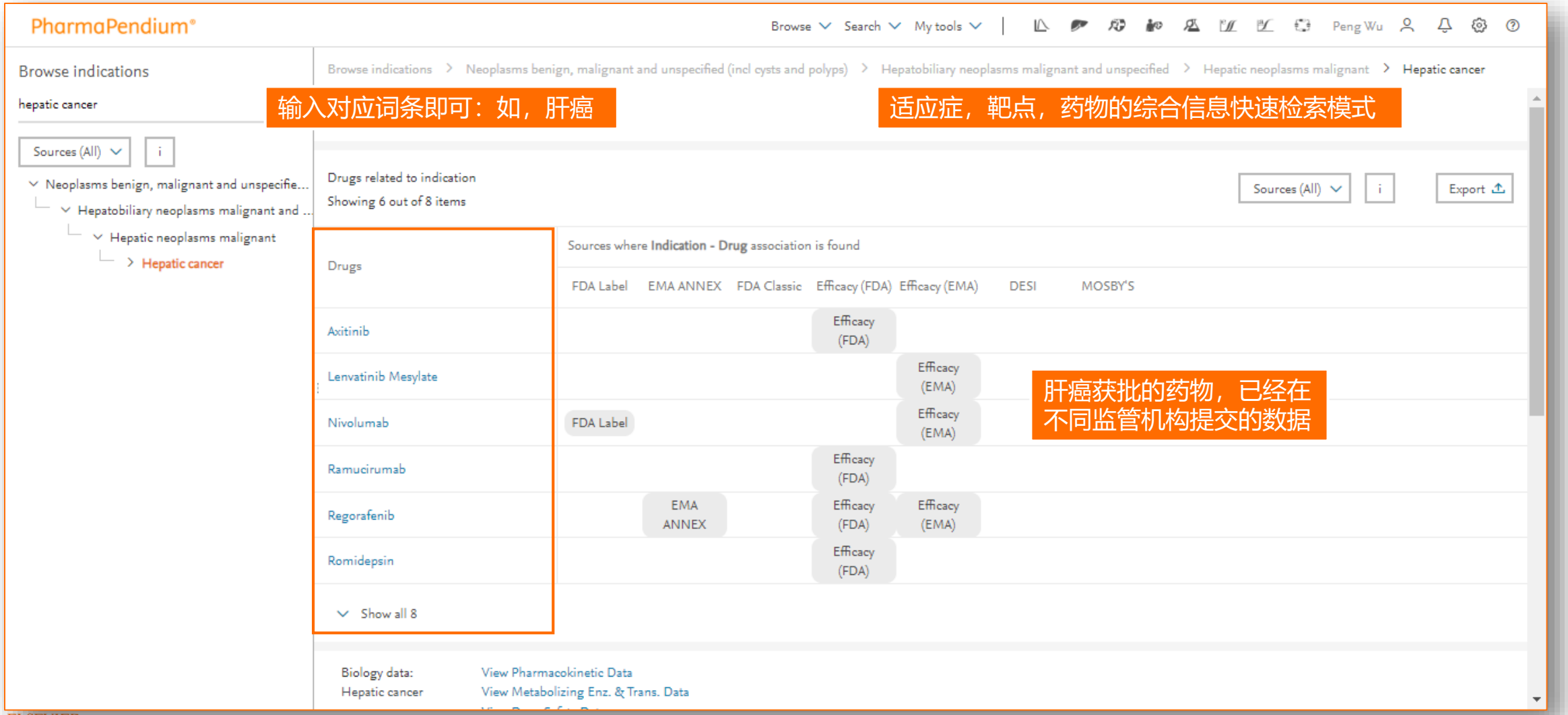
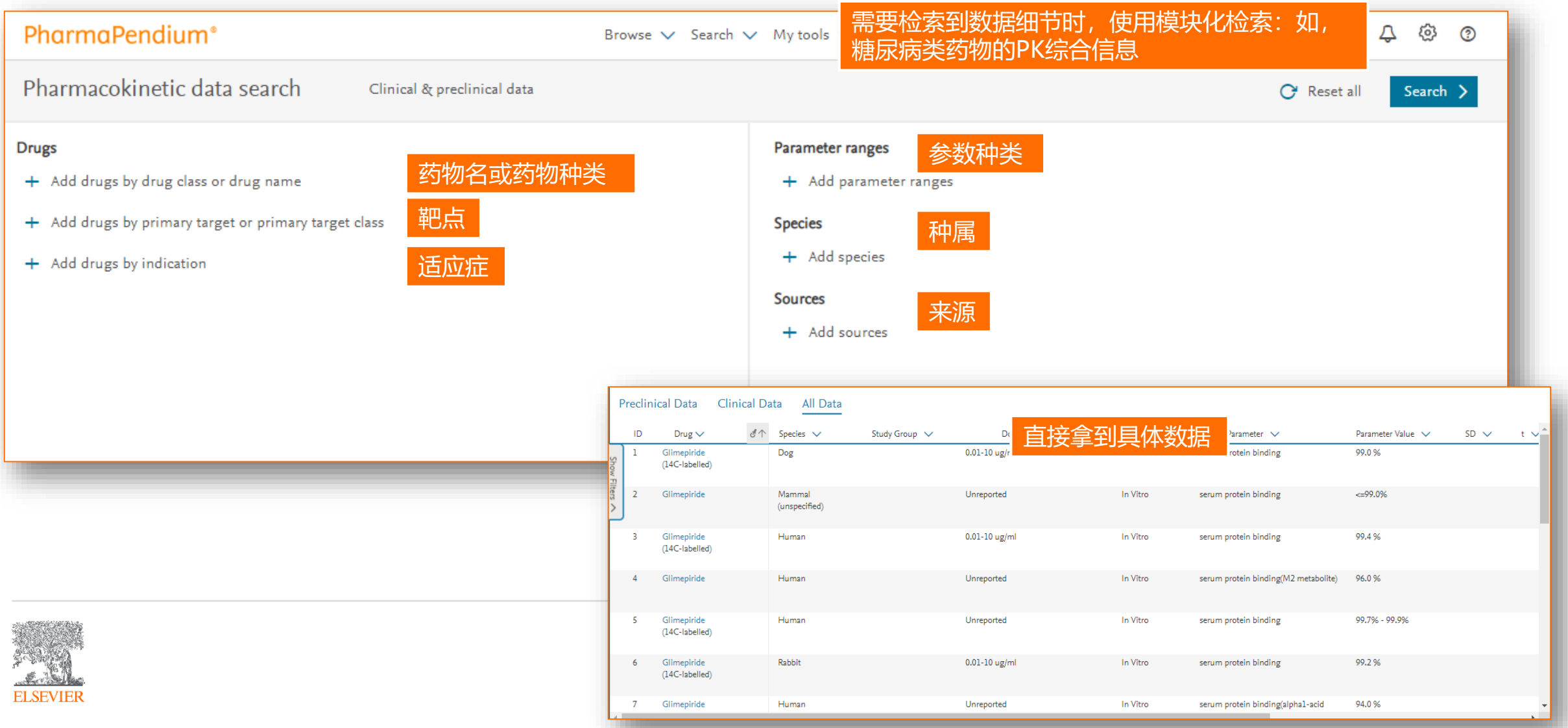
PharmaPendium中的基础检索----从适应症角度出发的检索



PharmaPendium中的基础检索---不同数据类型出发的模块化检索



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

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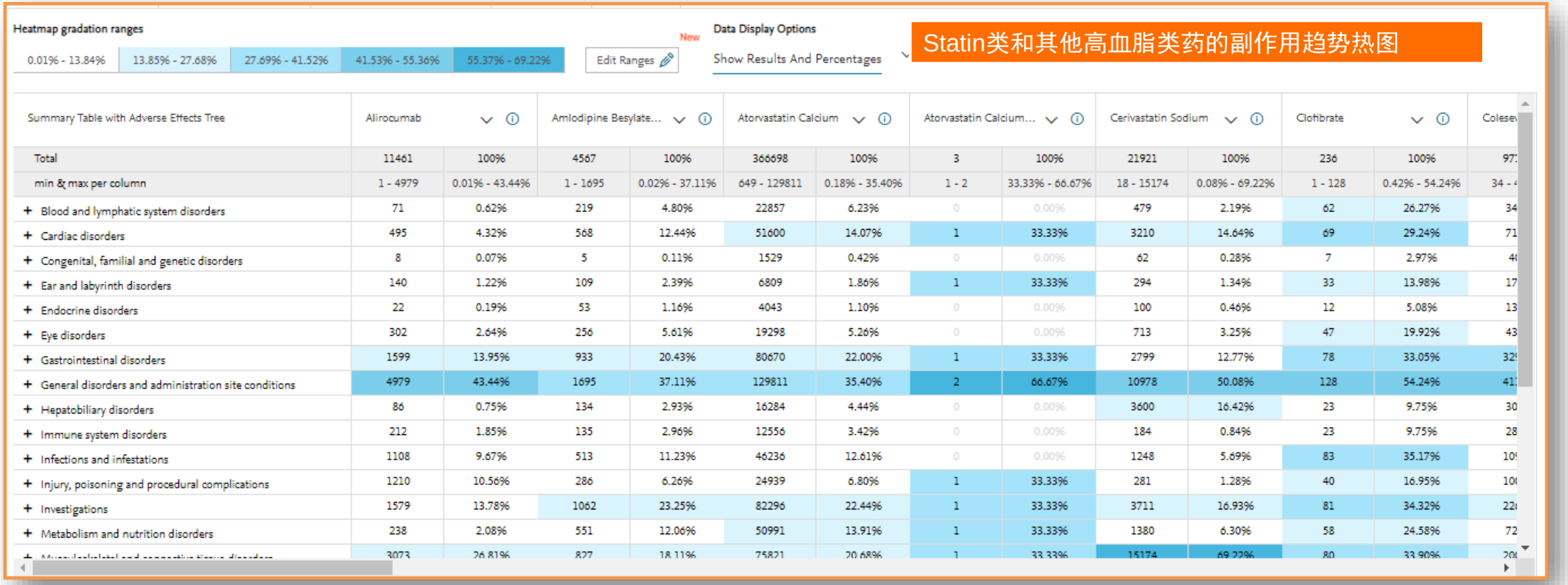
PharmaPendium中的基础应用---副作用分析



Heatmap gradation ranges

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

Edit Ranges (New)

Data Display Options: Show Results And Percentages

Statin类和其他高血脂类药的副作用趋势热图

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

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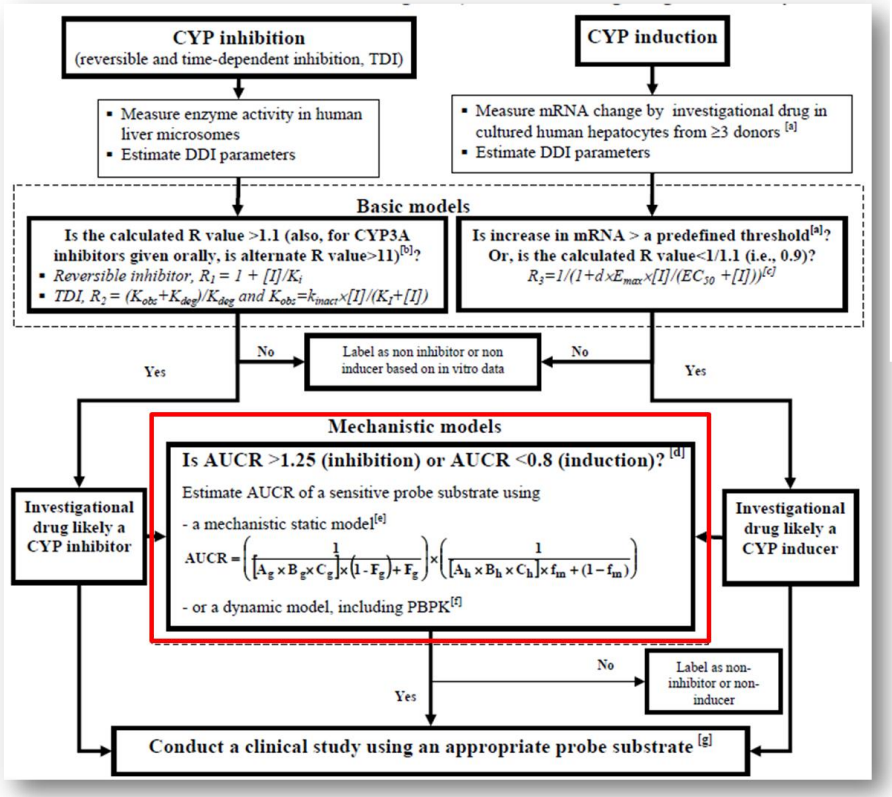
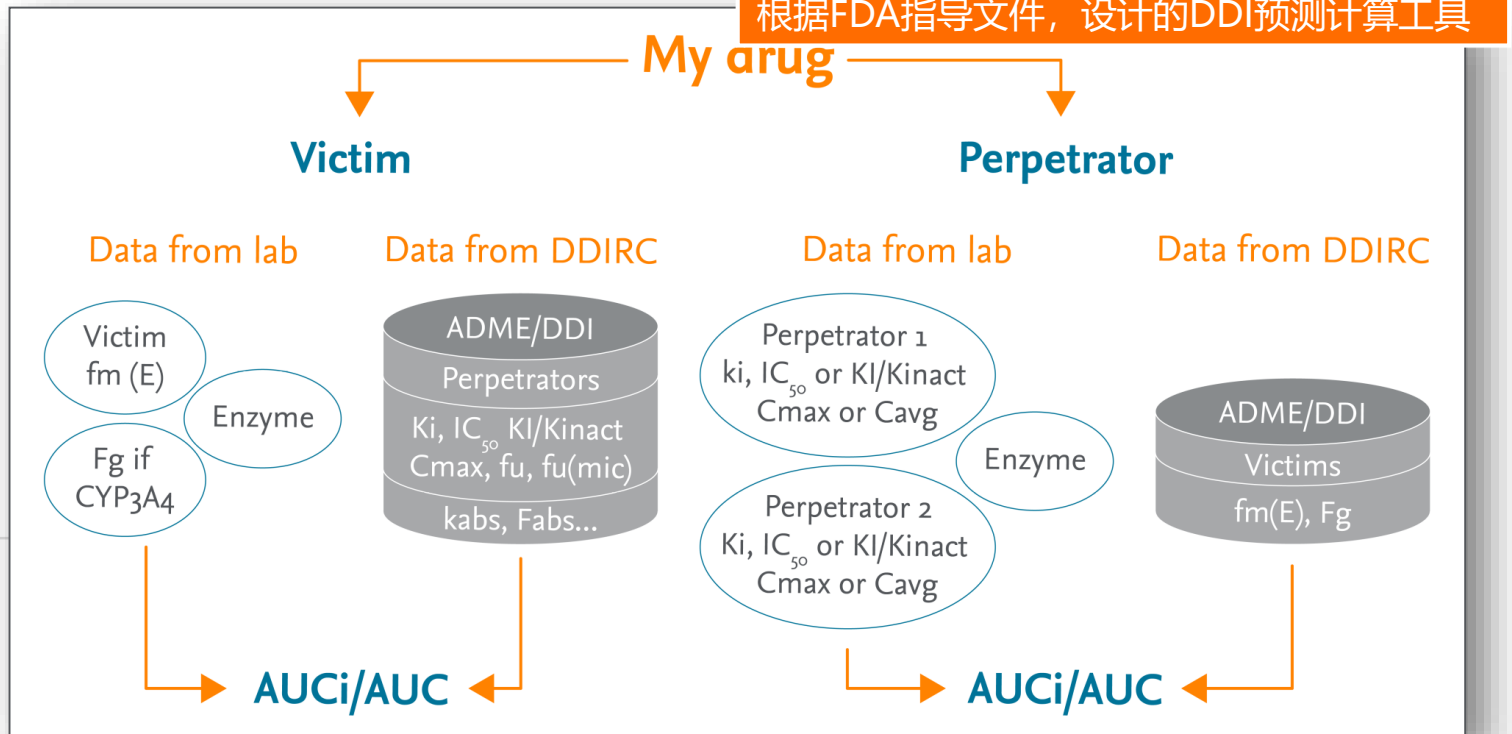
PharmaPendium中的进阶模块--- DDI预测计算



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

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

根据FDA指导文件，设计的DDI预测计算工具



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DDI预测计算结果—辅助实验方案制定

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

Results

Help on charts | Save

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min.	Max.	Mean	
1	(+)-Propoxyphene 91412 Analgesic: narcotic/opiate Dev.: + Drug Type: Approved	Multiple			4	1.061	1.554	1.308	
2	(+)-Warfarin 162426 Antithrombotic Dev.: + Drug Type: Experimental/Investigation	0.007 g			1	1.075	1.075	1.075	
3	(-)-Omeprazole 162827 Antiulcerative Proton pump inhibitor Dev.: - Drug Type: Approved	Multiple			88	1.022	1.078	1.051	
4	(-)-Warfarin 161583 Antithrombotic Dev.: - Drug Type: Experimental/Investigation	0.007 g			5	1.033	1.142	1.094	
5	AMG 487 628746 Dev.: - Drug Type: Unspecified	Multiple			3	2.82	18.223	9.607	6.42
6	Acamprosate 241873 Drug Type: Approved	Multiple			2646	1.012	1.271	1.1	0.058
7	Acetaminophen 99468 Analgesic: non narcotic	Multiple			72	4.048	4.134	4.088	0.025

Bar chart information

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

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

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

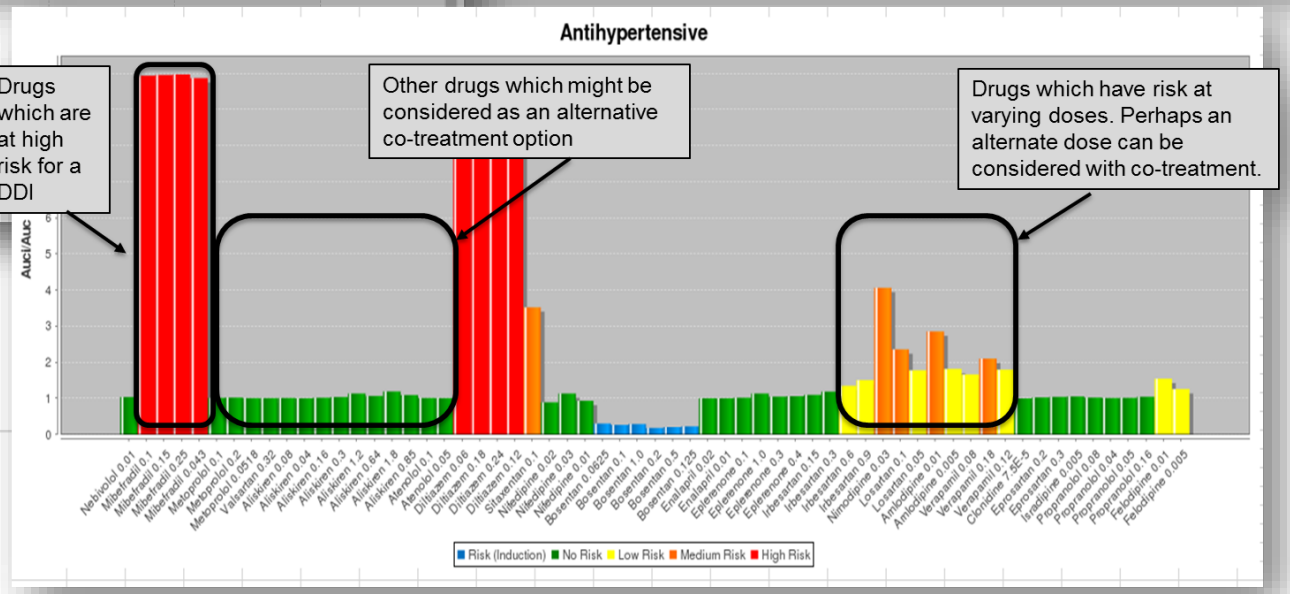
[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...

预测与上市药物DDI风险细节，包含剂量不同时的风险

Dose effect

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

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



总览各类型要与在研药物可能存在的风险

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

Accessing Marketed Drug Information from PharmaPendium to Inform PreClinical Safety

Duncan Armstrong
Preclinical Secondary Pharmacology, Novartis

Pooja Jain
Product Manager, PharmaPendium, Elsevier

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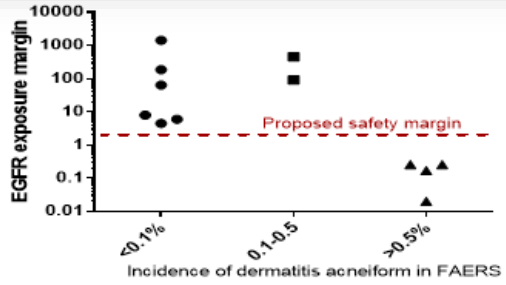
- List of marketed drugs with known ADR (QT prolongation, TdP)
- Effective Therapeutic Plasma Concentration $ETPC_{(unbound)}$ identified in the literature
- Activity in in vitro assay of hERG block measured

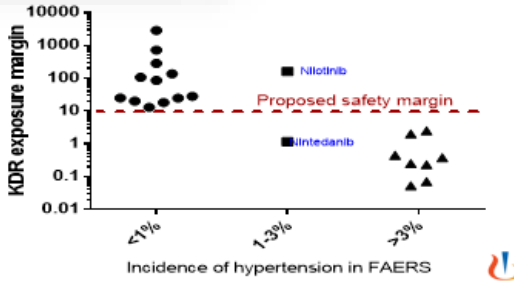
$$\text{Safety Margin} = \frac{\text{In vitro IC50}}{ETPC_{(unbound)}}$$

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

NOVARTIS

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





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FDA合作项目—通过上市后副作用分析临床前模型的敏感度

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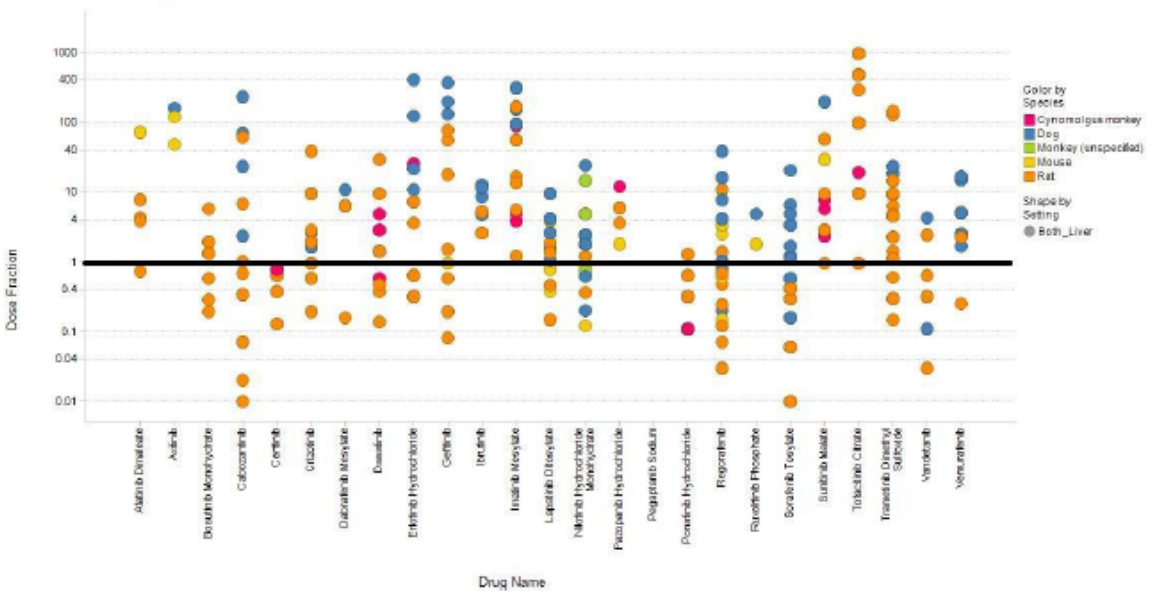
Liver Toxicities

Sorafenib, Sunitinib

Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	mg HED	DosFrac
Sorafenib Tosylate	Blood alkaline phosphatase increased	Rat	11 mg/kg/day	Repeated	Oral	0.96	0.001
Sorafenib Tosylate	Transaminases increased	Rat	11 mg/kg/day	Repeated	Oral	0.96	0.001
Sorafenib Tosylate	Blood alkaline phosphatase increased	Rat	5 mg/kg/day	Repeated	Oral	9.6	0.012
Sorafenib Tosylate	Liver disorder	Rat	5 mg/kg/day	Repeated	Oral	9.6	0.012
Sorafenib Tosylate	Liver function test abnormal	Rat	5 mg/kg/day	Repeated	Oral	9.6	0.012
Sorafenib Tosylate	Transaminases increased	Rat	5 mg/kg/day	Repeated	Oral	9.6	0.012
Sorafenib Tosylate	Hepatic necrosis	Rat	5.1 mg/kg/day	Repeated	Oral	48.96	0.061
Sorafenib Tosylate	Liver disorder	Rat	5.1 mg/kg/day	Repeated	Oral	48.96	0.061
Sorafenib Tosylate	Biopsy bile duct abnormal	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Biopsy bile duct abnormal	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Hepatic cirrhosis	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Hepatic cirrhosis	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Liver disorder	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Liver disorder	Dog	6 mg/kg/day	Repeated	Oral	129.6	0.162
Sorafenib Tosylate	Liver disorder	Rat	44.3 mg/kg/day	Repeated	Oral	329.28	0.412
Sorafenib Tosylate	Liver function test abnormal	Rat	44.3 mg/kg/day	Repeated	Oral	329.28	0.412
Sorafenib Tosylate	Liver function test abnormal	Rat	44.3 mg/kg/day	Repeated	Oral	329.28	0.412
Sorafenib Tosylate	Blood bilirubin increased	Rat	45 mg/kg/day	Repeated	Oral	336	0.420
Sorafenib Tosylate	Liver disorder	Rat	45 mg/kg/day	Repeated	Oral	336	0.420
Sorafenib Tosylate	Liver disorder	Rat	45 mg/kg/day	Repeated	Oral	336	0.420
Sorafenib Tosylate	Transaminases increased	Rat	45 mg/kg/day	Repeated	Oral	336	0.420
Sorafenib Tosylate	Biopsy bile duct abnormal	Dog	24 mg/kg/day	Repeated	Oral	453.6	0.567
Sorafenib Tosylate	Blood alkaline phosphatase increased	Dog	24 mg/kg/day	Repeated	Oral	453.6	0.567
Sorafenib Tosylate	Hepatic cirrhosis	Dog	24 mg/kg/day	Repeated	Oral	453.6	0.567
Sorafenib Tosylate	Liver disorder	Dog	24 mg/kg/day	Repeated	Oral	453.6	0.567
Sorafenib Tosylate	Transaminases increased	Dog	24 mg/kg/day	Repeated	Oral	453.6	0.567
Sunitinib Malate	Transaminases increased	Rat	5 mg/kg/day	Repeated	Oral	48	0.960
Sorafenib Tosylate	Alanine aminotransferase increased	Human	400 mg/twice a day	Repeated	Oral	800	1.000
Sorafenib Tosylate	Aspartate aminotransferase increased	Human	400 mg/twice a day	Repeated	Oral	800	1.000
Sorafenib Tosylate	Blood bilirubin increased	Human	400 mg/twice a day	Repeated	Oral	800	1.000
Sorafenib Tosylate	Transaminases increased	Human	400 mg/twice a day	Repeated	Oral	800	1.000
Sunitinib Malate	Alanine aminotransferase abnormal	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Alanine aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Alanine aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Alanine aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Alanine aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Aspartate aminotransferase abnormal	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Aspartate aminotransferase abnormal	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Aspartate aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Aspartate aminotransferase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Blood alkaline phosphatase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Blood alkaline phosphatase increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Blood bilirubin increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Blood bilirubin increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Blood bilirubin unconjugated increased	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Cholecystitis	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Cholecystitis acute	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Cholelithiasis	Human	50 mg/day	Repeated	Oral	50	1.000
Sunitinib Malate	Hepatic failure	Human	50 mg/day	Repeated	Oral	50	1.000

Non-Clinical Liver Toxicities

All TKI drugs



- All of the 26 TKI drugs elicited hepatotoxicity in clinical trials; only Nintedanib did not do so also in non-clinical studies
- Pegaptanib showed non-clinical hepatotoxicity at a Dose Fraction of 16,000 (off scale)

Conclusions

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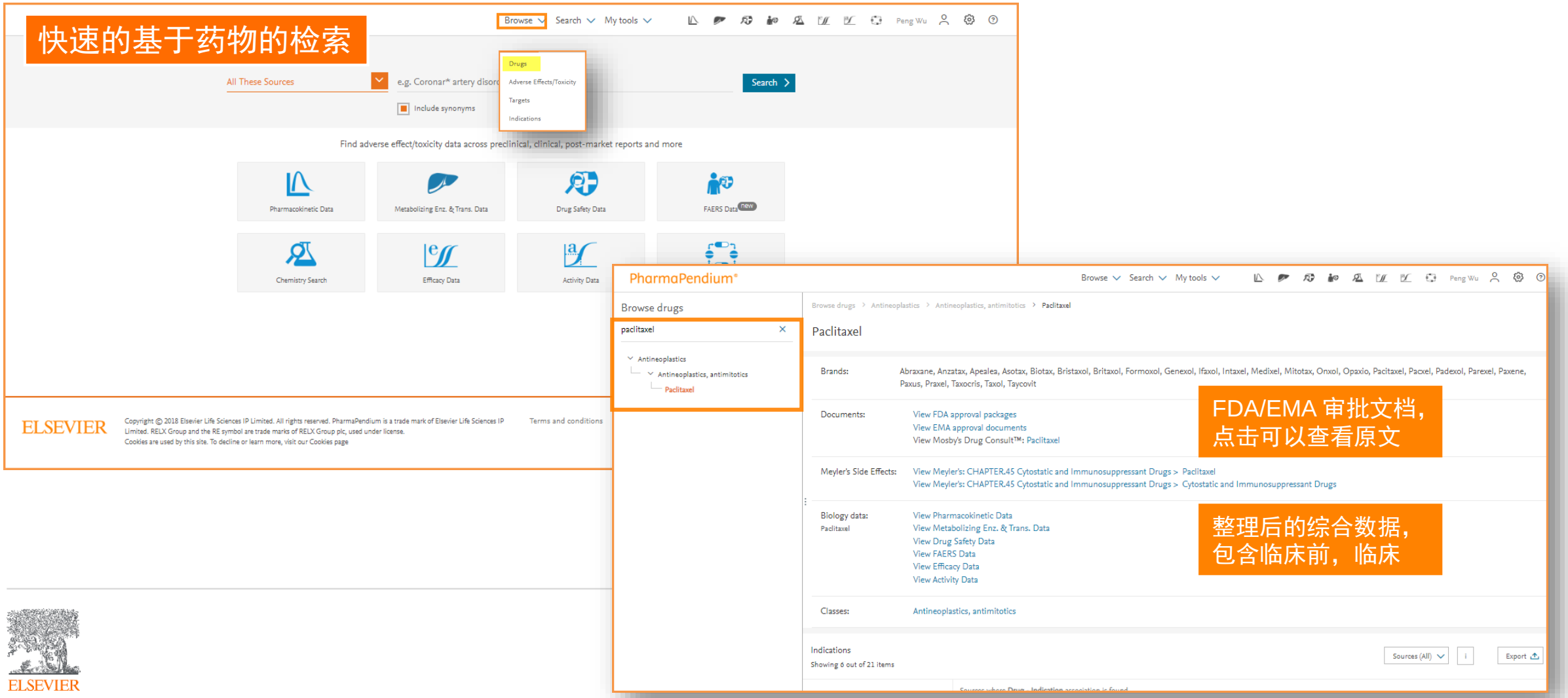
    - DDI

药物安全性，药效，DMPK数据的获取

Case 1： Paclitaxel 临床前信息检索
Case 2：他汀类药物的临床前毒理药理信息
Case 3： QT延长趋势研究

Case 1： 紫杉醇（Paclitaxel）临床前信息检索



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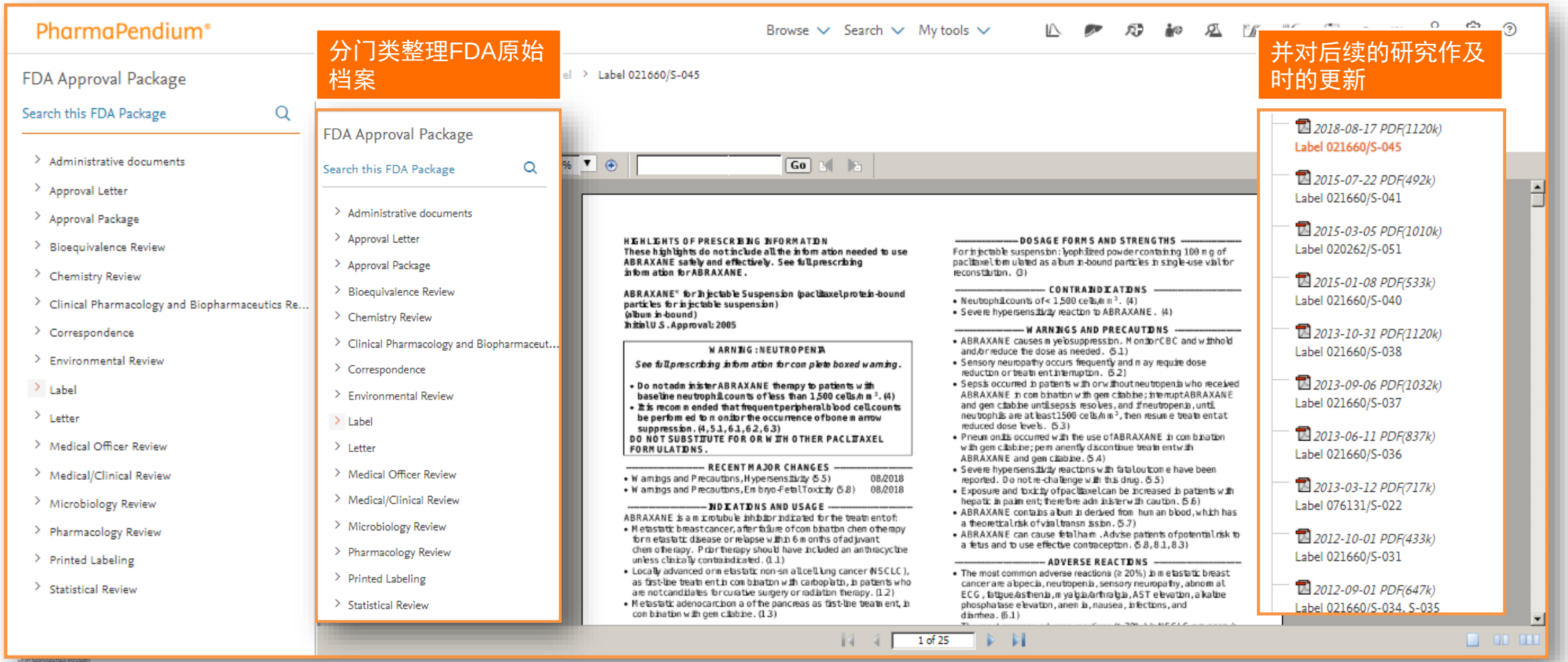
对原始文献的便捷查询



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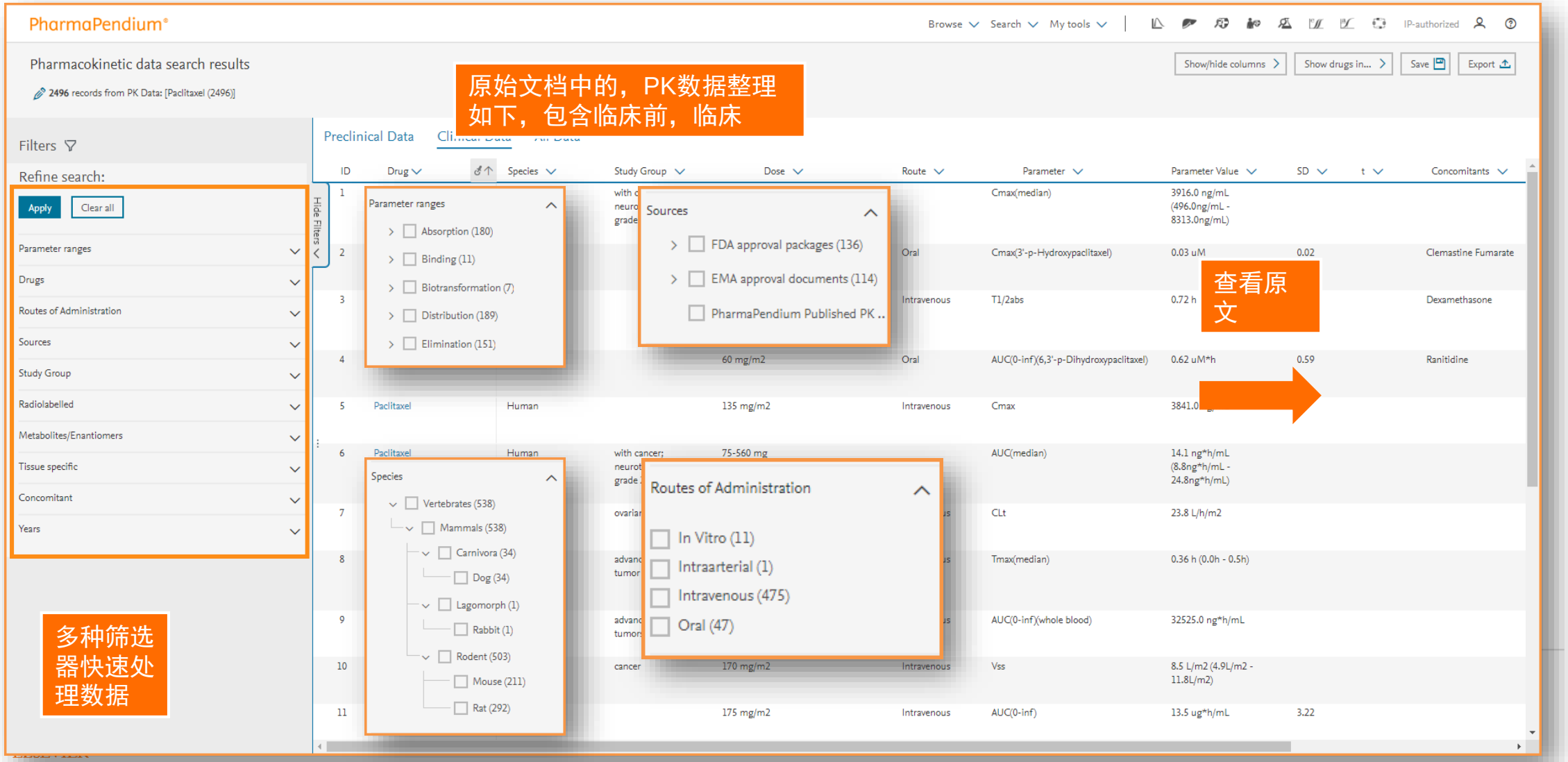
原始文档--临床前信息整理，便于分析处理

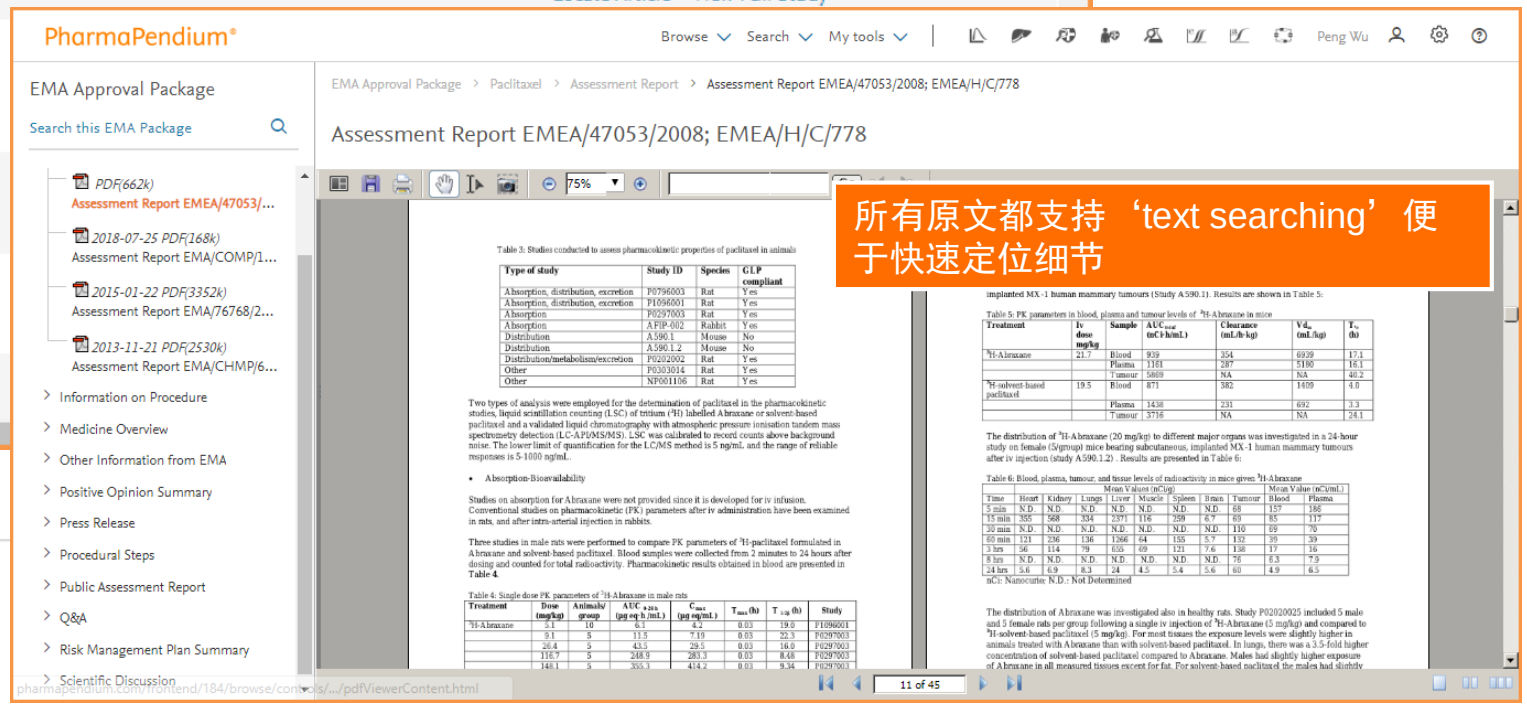


更便捷的追踪原文

Preclinical Data | Clinical Data | All Data

Hide Filters

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



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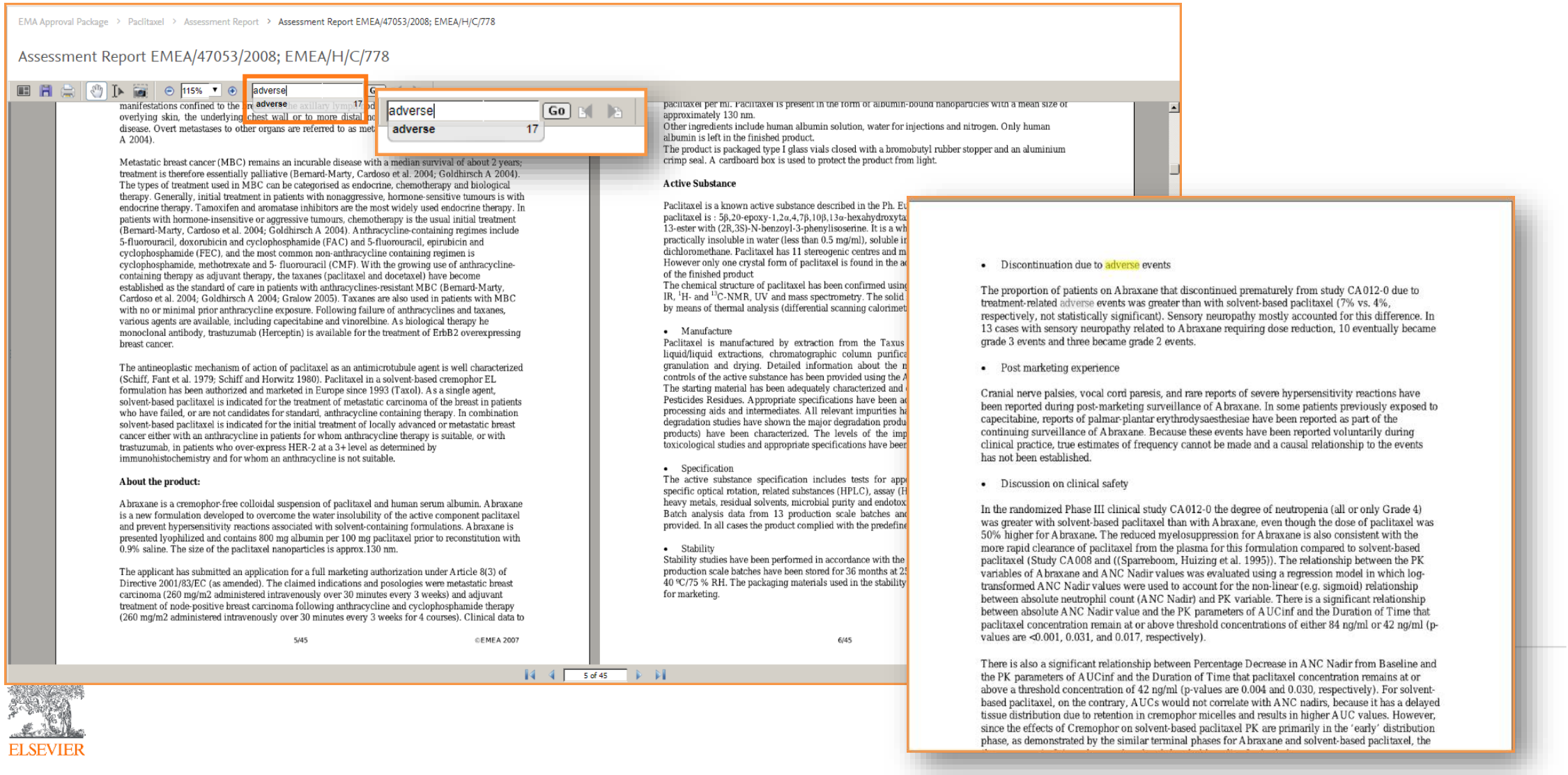
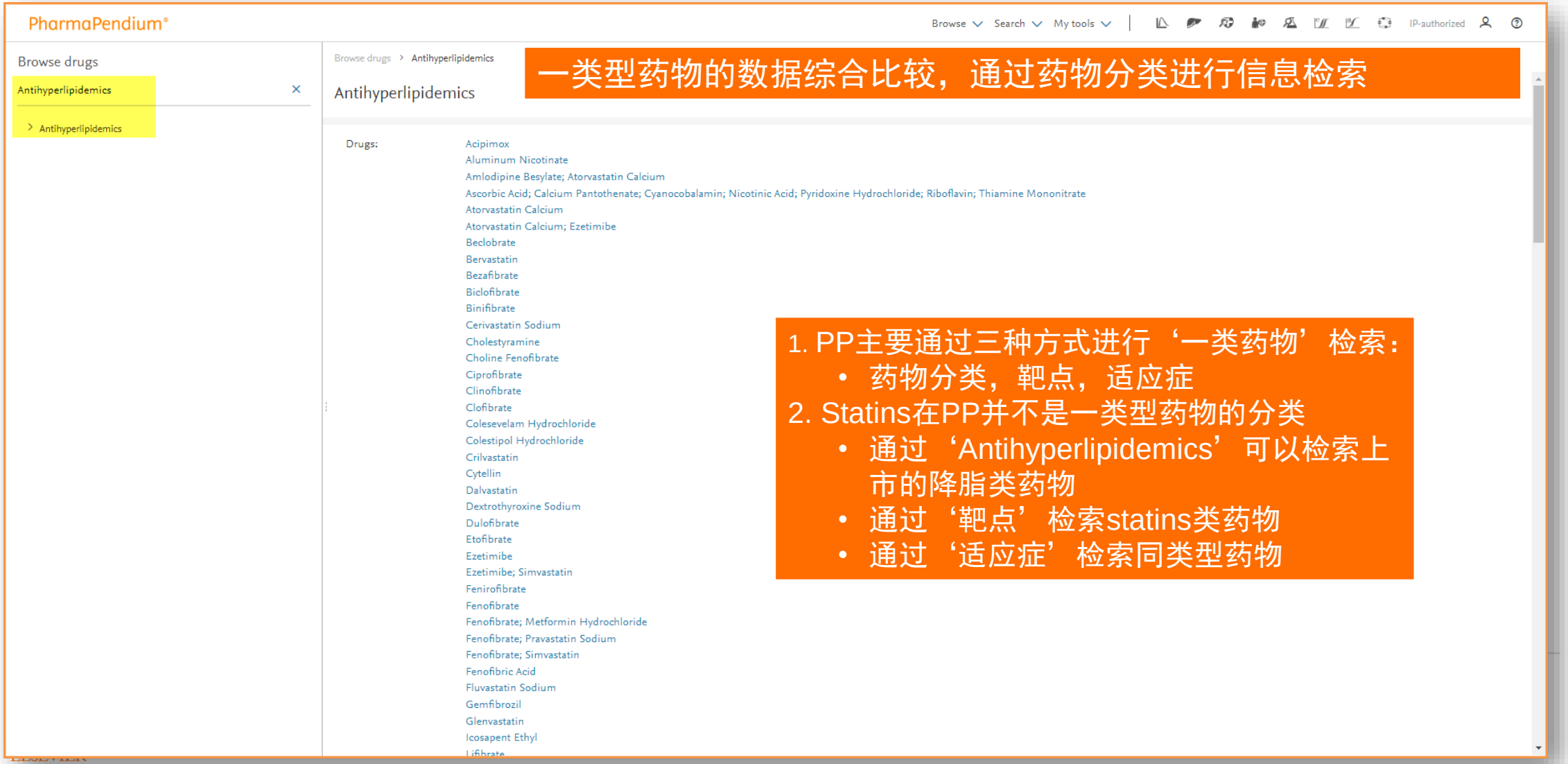
原文界面‘关键词’直接检索

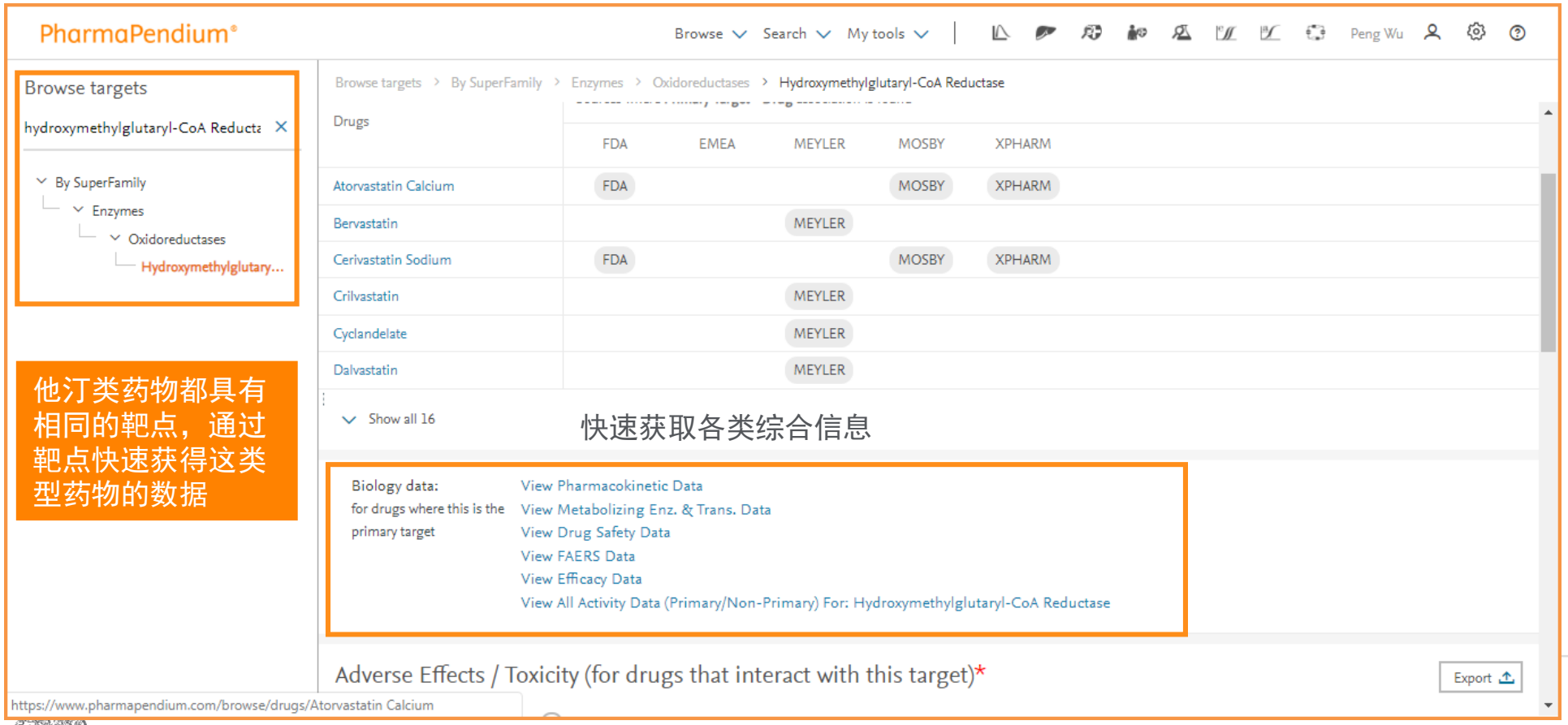


Case 2：他汀类药物的临床前毒理药理信息



通过靶点检索对应药物

通过作用机制的靶点，可以快速索引到对应上市后药物



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Statin类药物数据比较-药效

Efficacy data search results

药效信息

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

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

Preclinical Data | Clinical Data

Show Filters

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

以上数据即可导出规整的Excel表格便于分析

Export date: 22-04-2019
Efficacy Data Search Results For: Drugs: [Cerivastatin Sodium (1770) OR Atorvastatin Calcium (6372) OR Pitavastatin (92) OR Fluvast
Total results: 24829
Sort order: Drug (Ascending); Indication Type (Ascending); Endpoint Type (Ascending);

Drug	Study Numb	Phase	Mono/Combinatio	Study Design	Specie	Sex	Age	Indication Type	Indication	th	Rou	Dose Regimen	Dose Freque
Atorvastatin Calcium		Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Open-label crossover study	Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 or 80 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	0 mg	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	40 mg	
Atorvastatin Calcium		Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Open-label crossover study	Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	80 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	0 mg	
Atorvastatin Calcium	Study 2	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium	Study 1	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Combination	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia		Oral	0 mg/day; slovastatin 20 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	0	
Atorvastatin Calcium		Not specified	Monotherapy		Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	0.0	
Atorvastatin Calcium		Not specified	Monotherapy	24 controlled trials	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	80 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	0 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy		Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	20 mg	
Atorvastatin Calcium		Not specified	Monotherapy	Double-blind, placebo-controlled study followe	Human	Both	Child-adolesce	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg QD for the first 4 weeks a	Once a day
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, Double-Blind, Randomized, Activ	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	10 mg daily	
Atorvastatin Calcium		Not specified	Monotherapy	Open-label crossover study	Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	80 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	0	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	40 mg/day	
Atorvastatin Calcium	Study 3	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	0	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	10 mg	
Atorvastatin Calcium		Not specified	Monotherapy	Open-label crossover study	Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 or 80 mg/day	
Atorvastatin Calcium		Not specified	Combination	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Hyperlipidemia		Oral	0 mg/day; slovastatin 20 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, Double-Blind, Randomized, Activ	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	0 mg daily + Simvastatin 10 mg/	
Atorvastatin Calcium	Study 3	Not specified	Monotherapy	Double-Blind, Randomized, Active-Controlled	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	Two multicenter, placebo-controlled, dose-res	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	0	
Atorvastatin Calcium		Not specified	Monotherapy		Human	Both		Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	10 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	24 controlled trials	Human	Both	Adult-aged	Hyperlipidemia	Inhibitor of HMG-CoA reductase (statin) indicated as an a		Oral	80 mg/day	
Atorvastatin Calcium		Not specified	Monotherapy	multicenter, placebo-controlled, dose-response	Human		Adult-aged	Hyperlipidemia	Primary Hyperlipidemia		Oral	10 mg	

Efficacy Data

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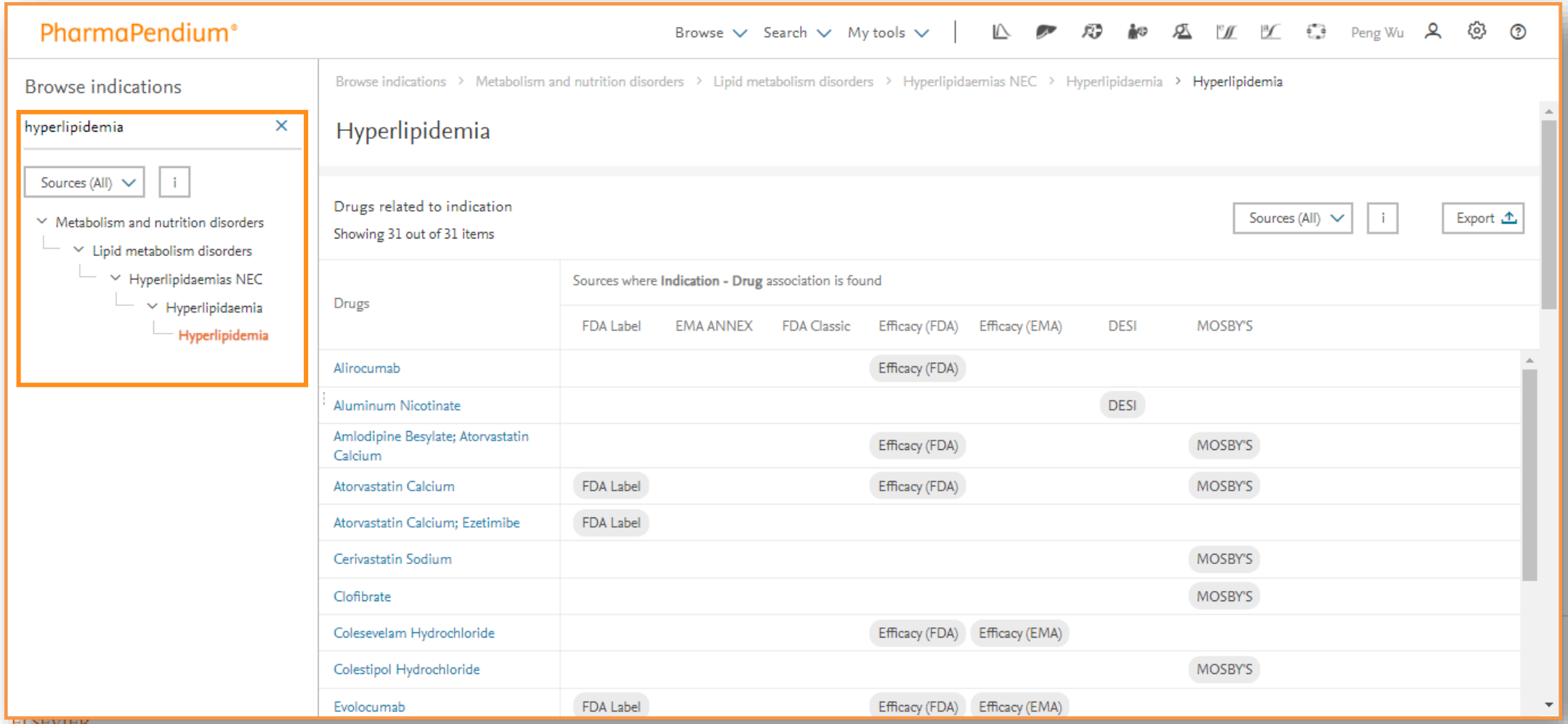
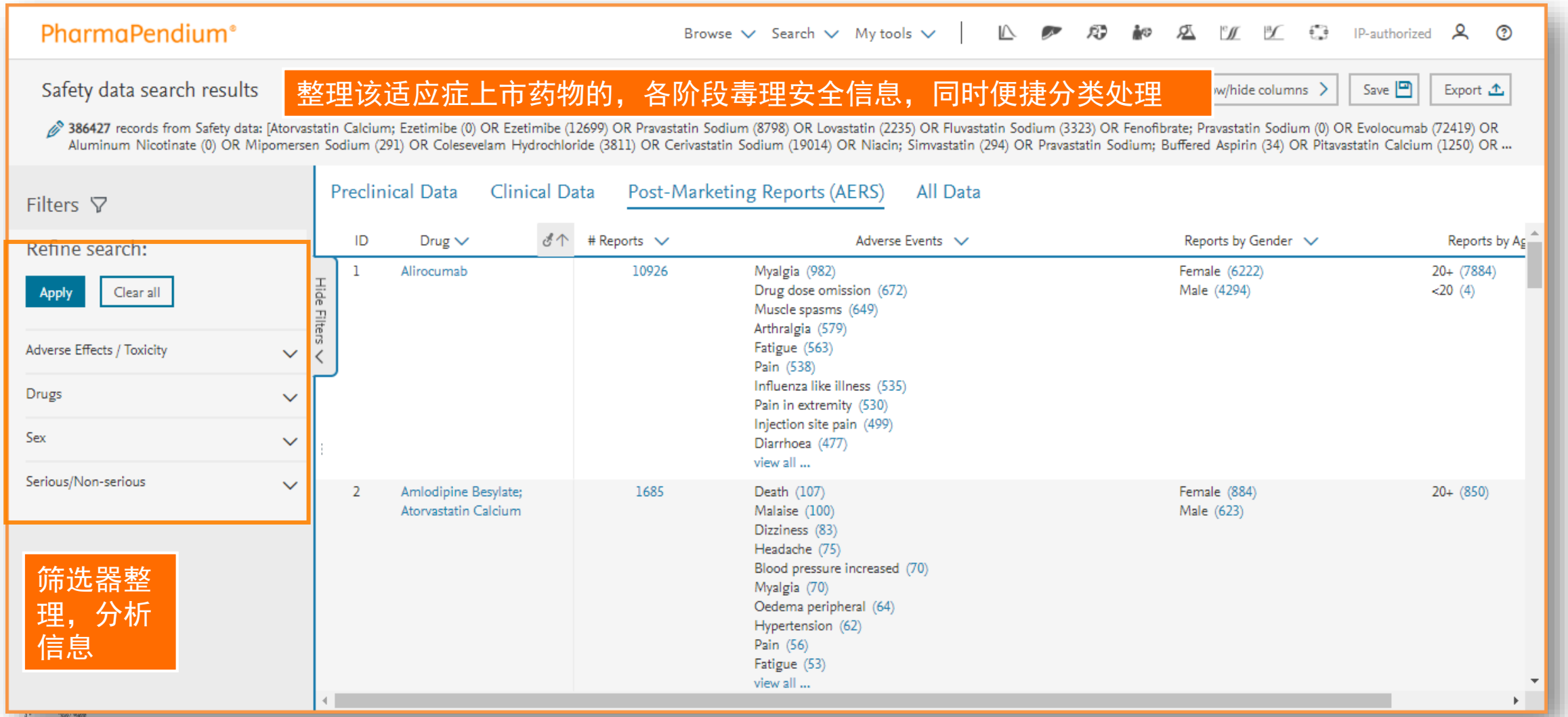
通过“适应症”获取相关上市药物信息

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



整理所有‘高血脂’类药物的毒理/副作用信息



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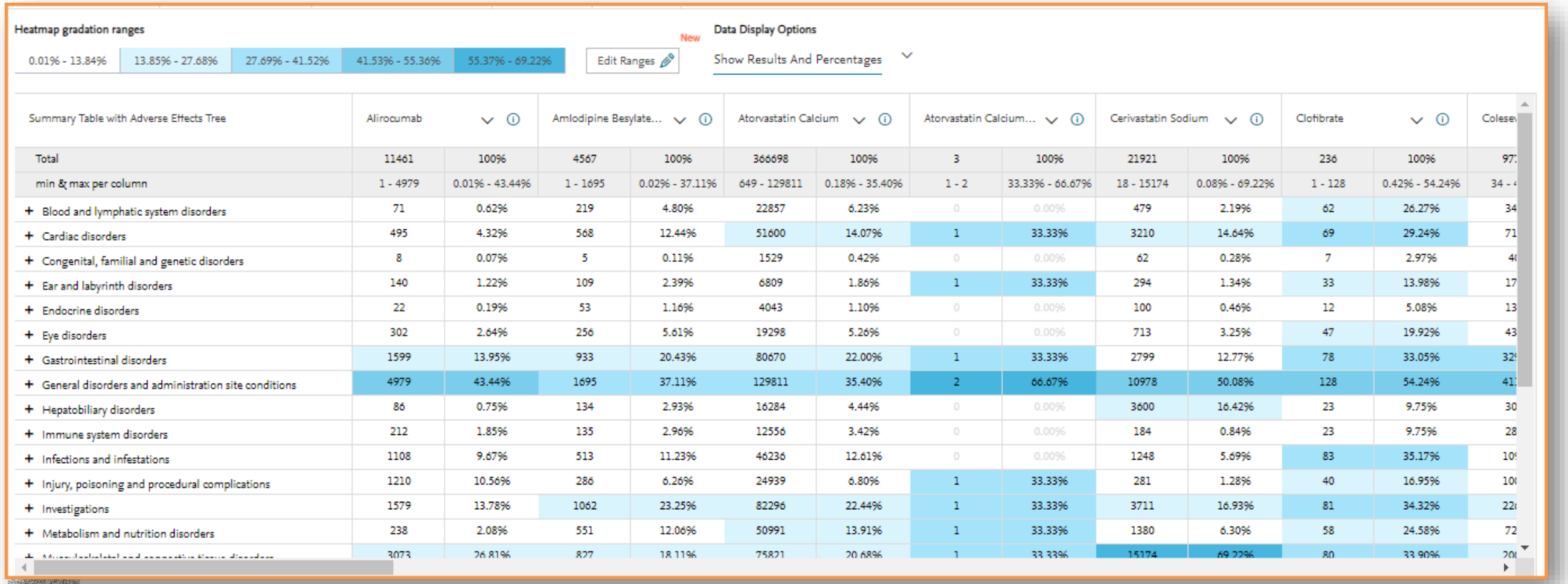
副作用分布研究，辅助临床科研

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



Heatmap gradation ranges

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

Edit Ranges

New

Data Display Options

Show Results And Percentages

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

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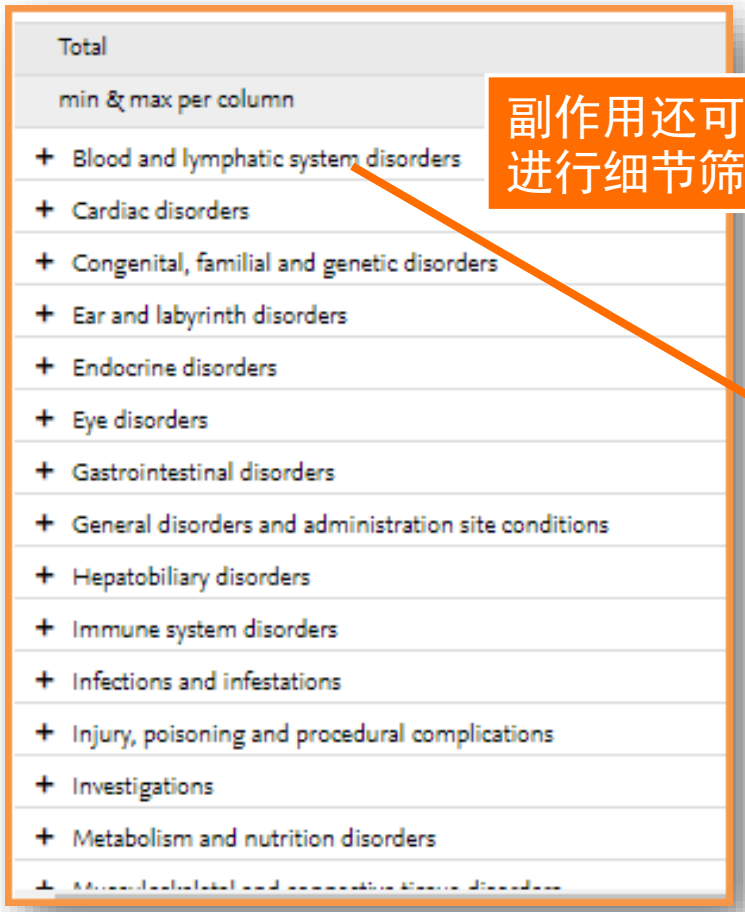
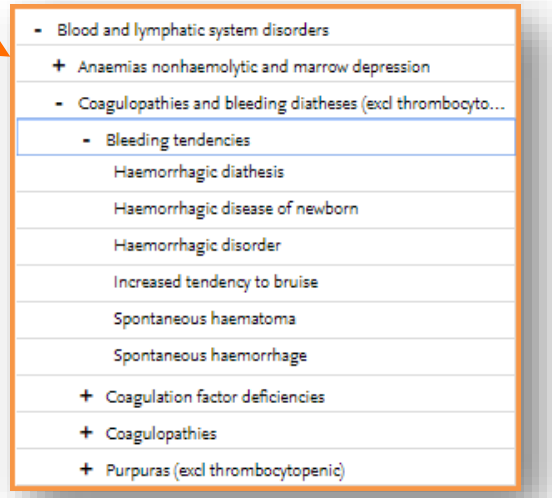
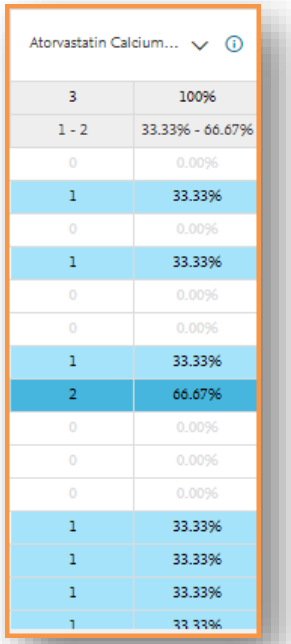
副作用分布细节—层级展示辅助安评分析



副作用还可以进行细节筛选



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



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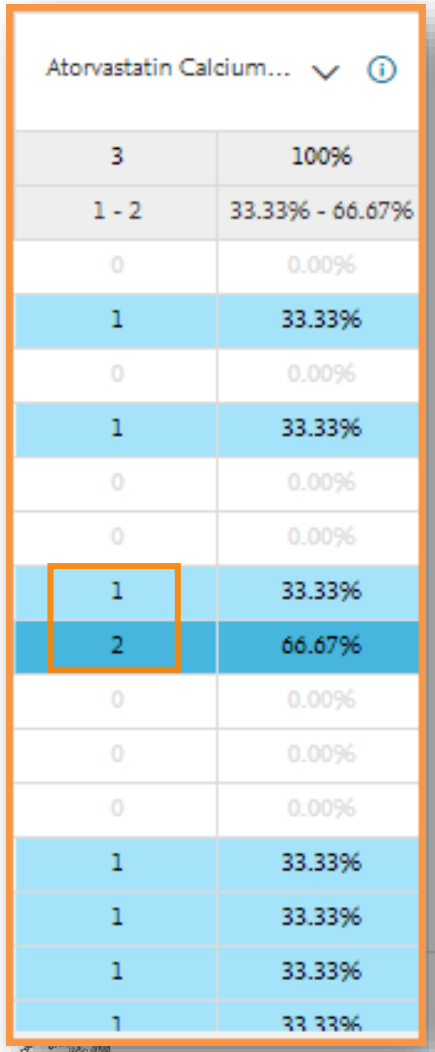
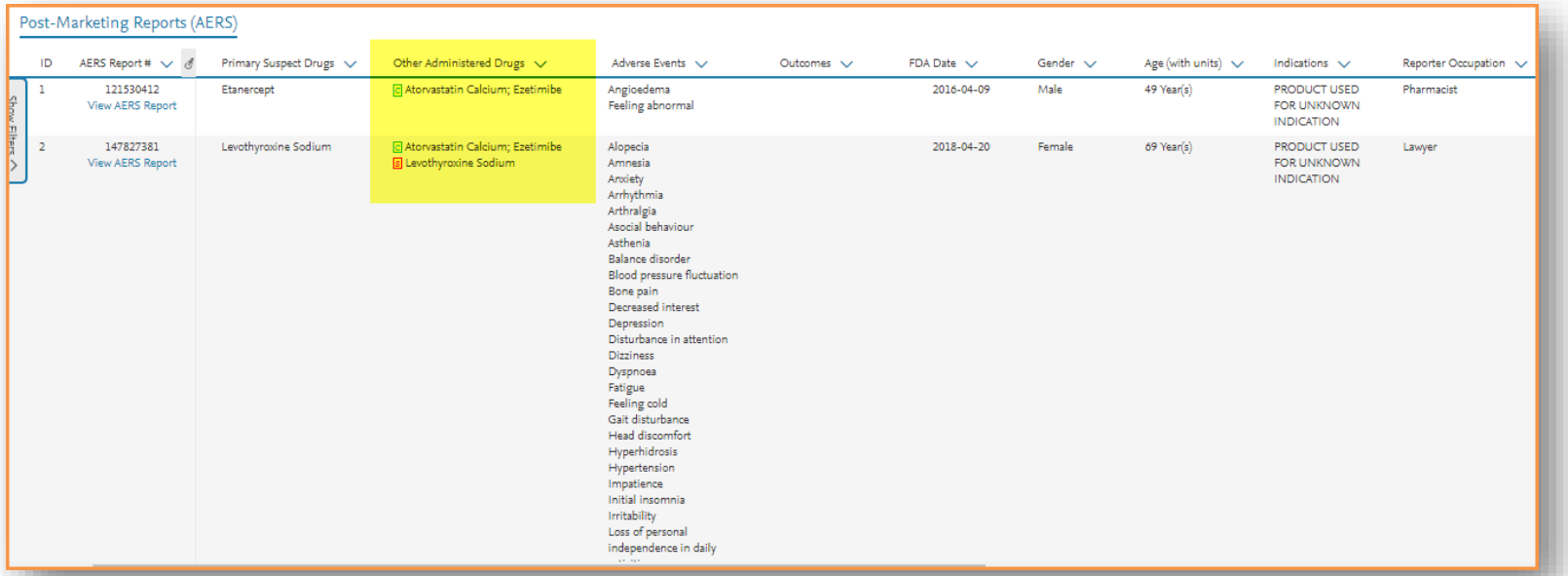
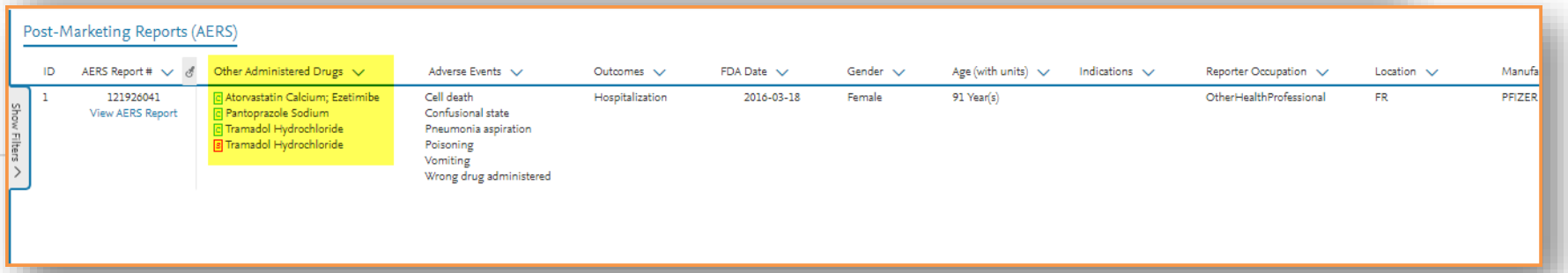
副作用分布细节—具体细节辅助DDI研究

每个数据可以点击查看副作用报告细节，便于进行‘DDI’相关研究

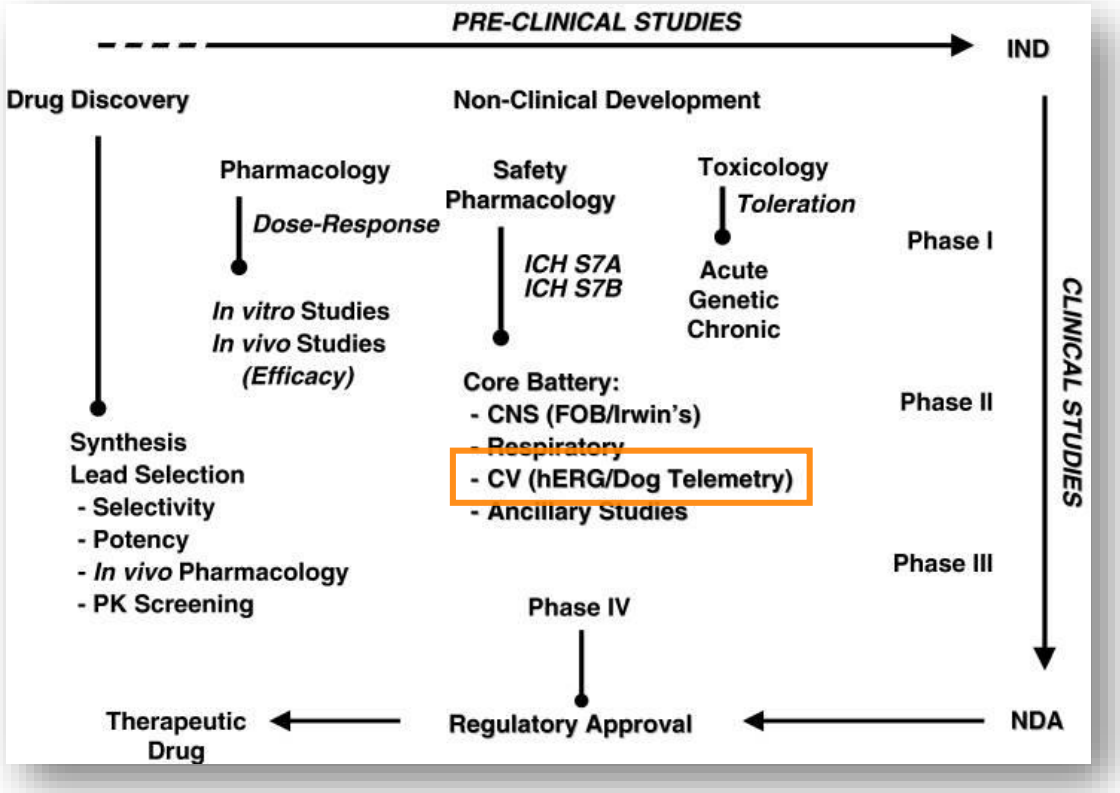




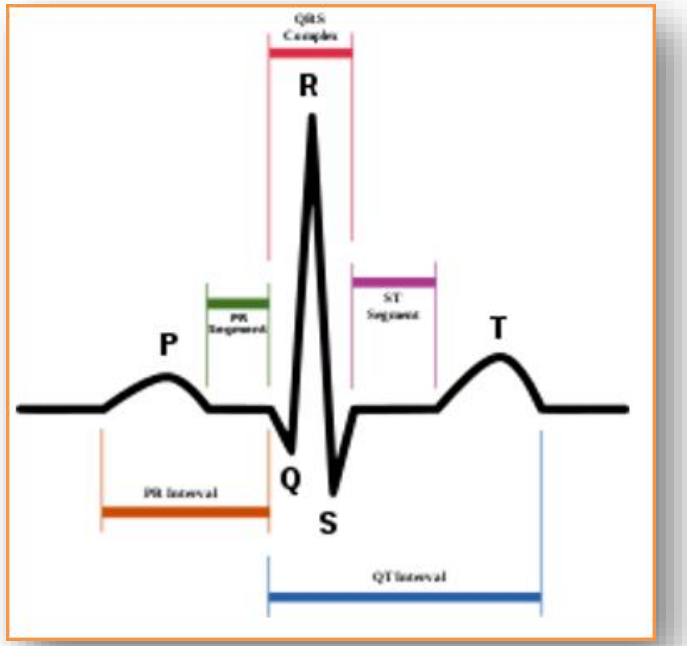


Case 3: QT延长趋势研究

安全药理学：QT 信号通路延长趋势研究



QT interval （QT间隔） 在心脏心电周期中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.

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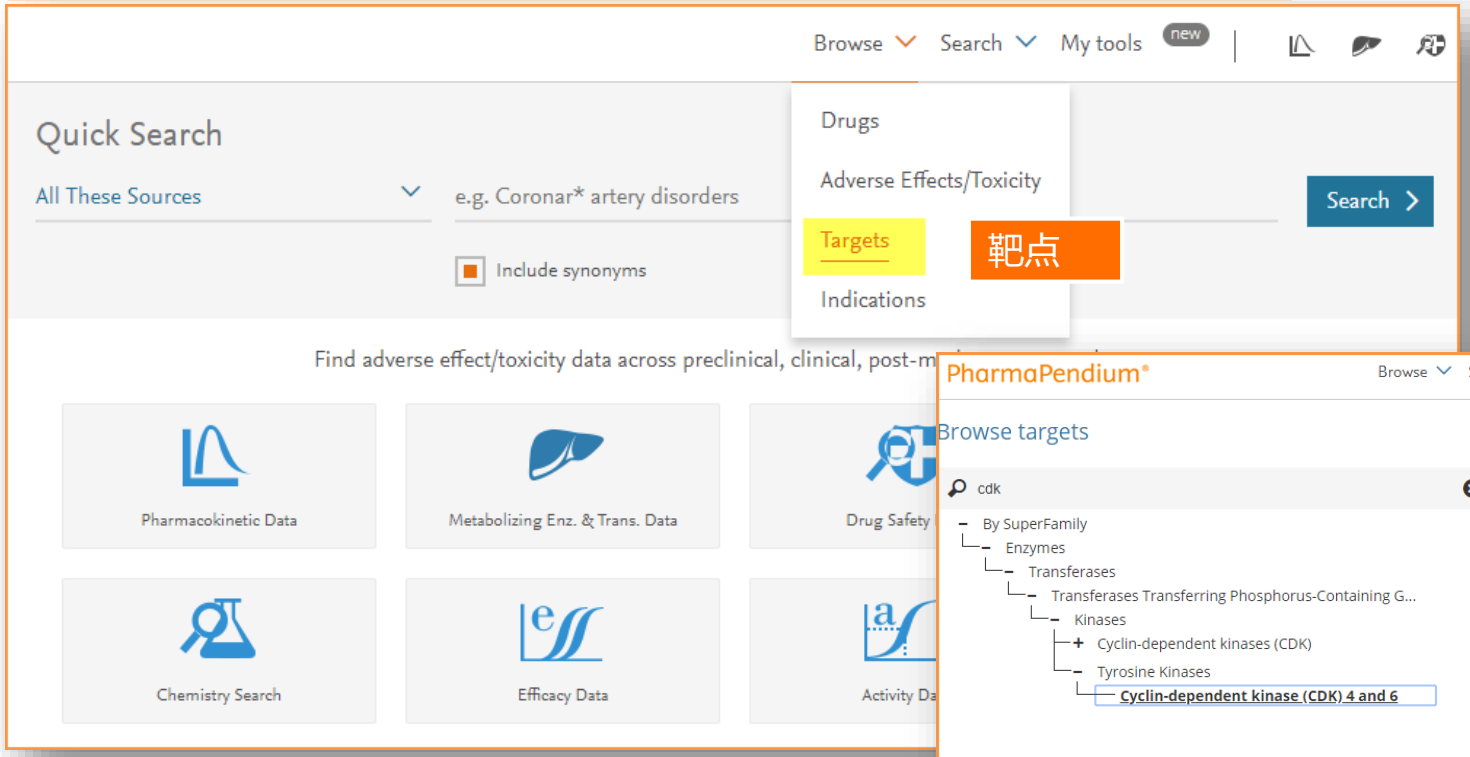
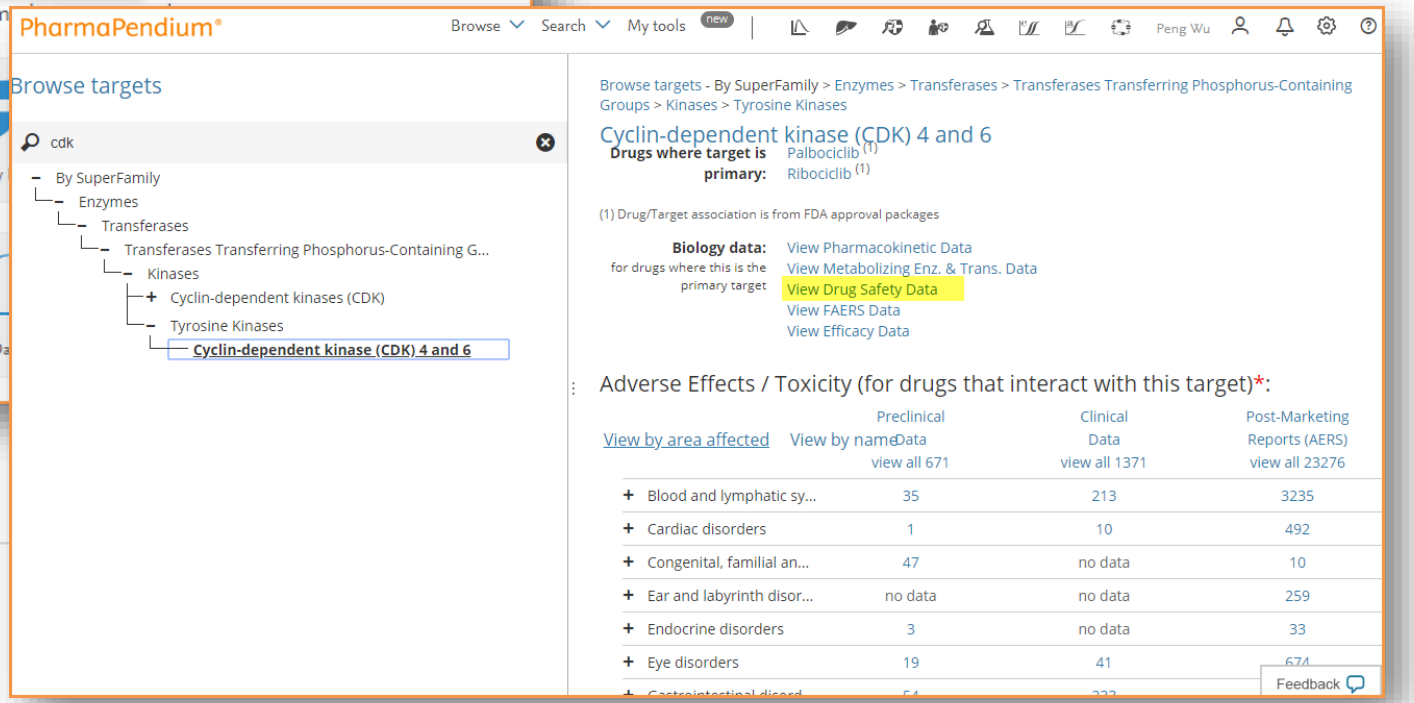
基于靶点的药理信息整理

如何从靶点（如，CDK）出发收集信息，支持QT毒理相关研究？



基于靶点的上市药物安全信息归纳



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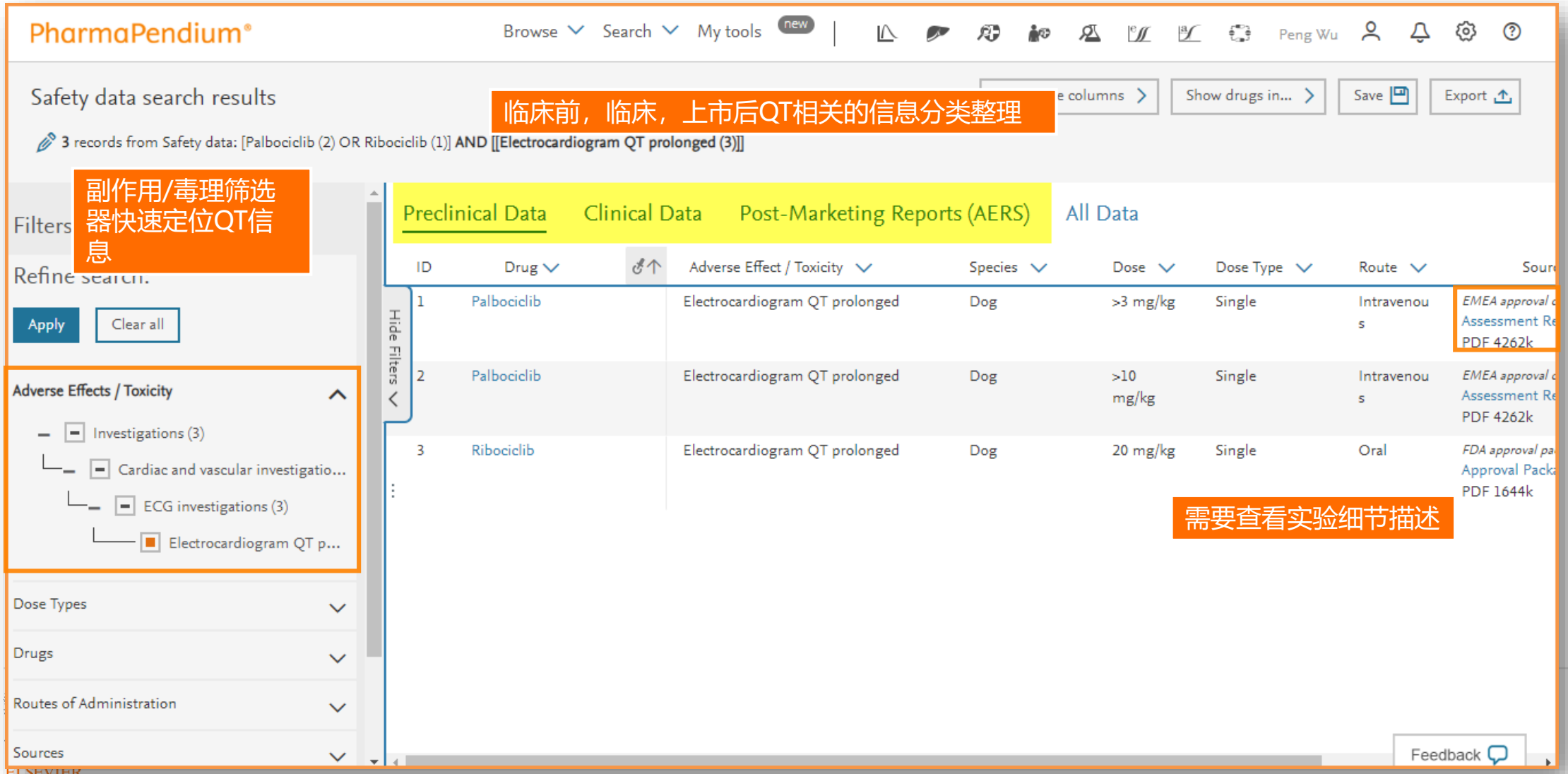
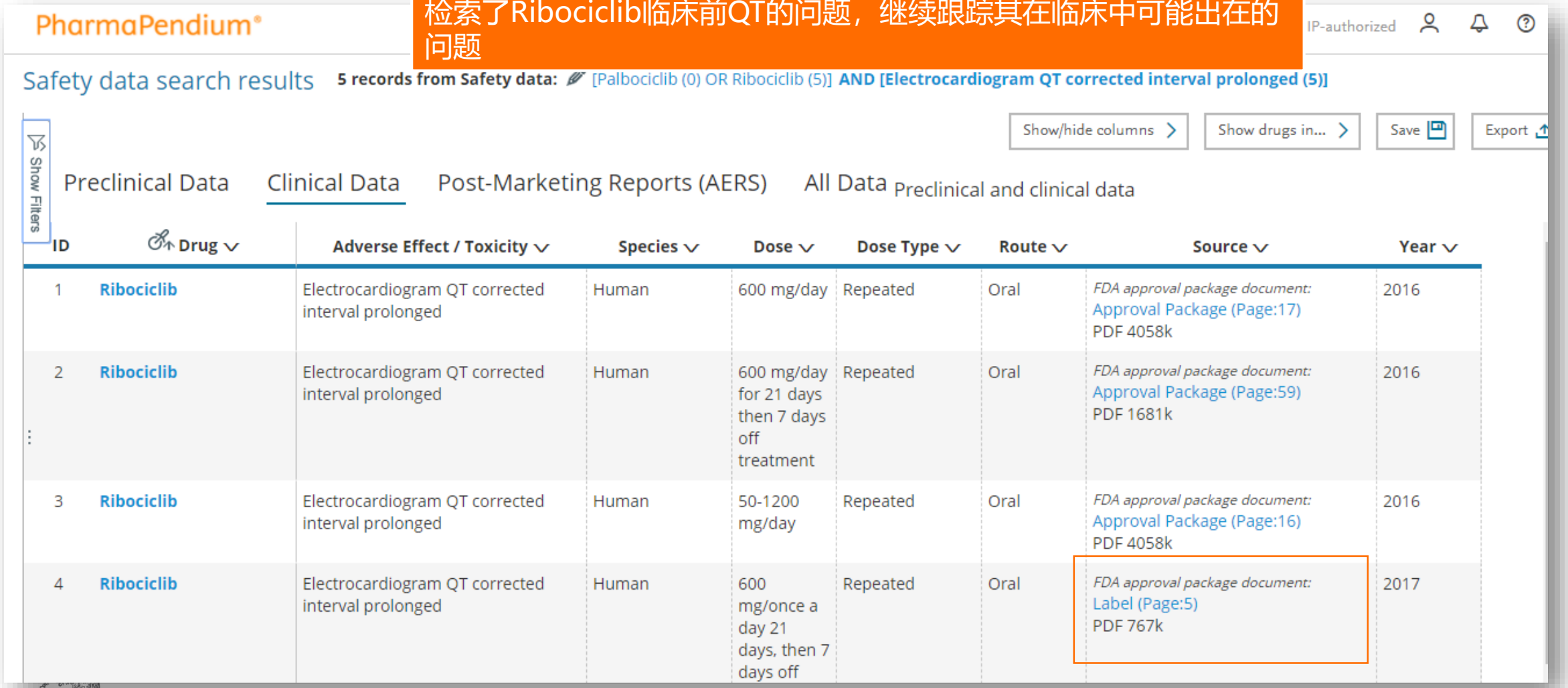
筛选-快速分类Safety中的QT研究信息



继续查看临床中的QT信息

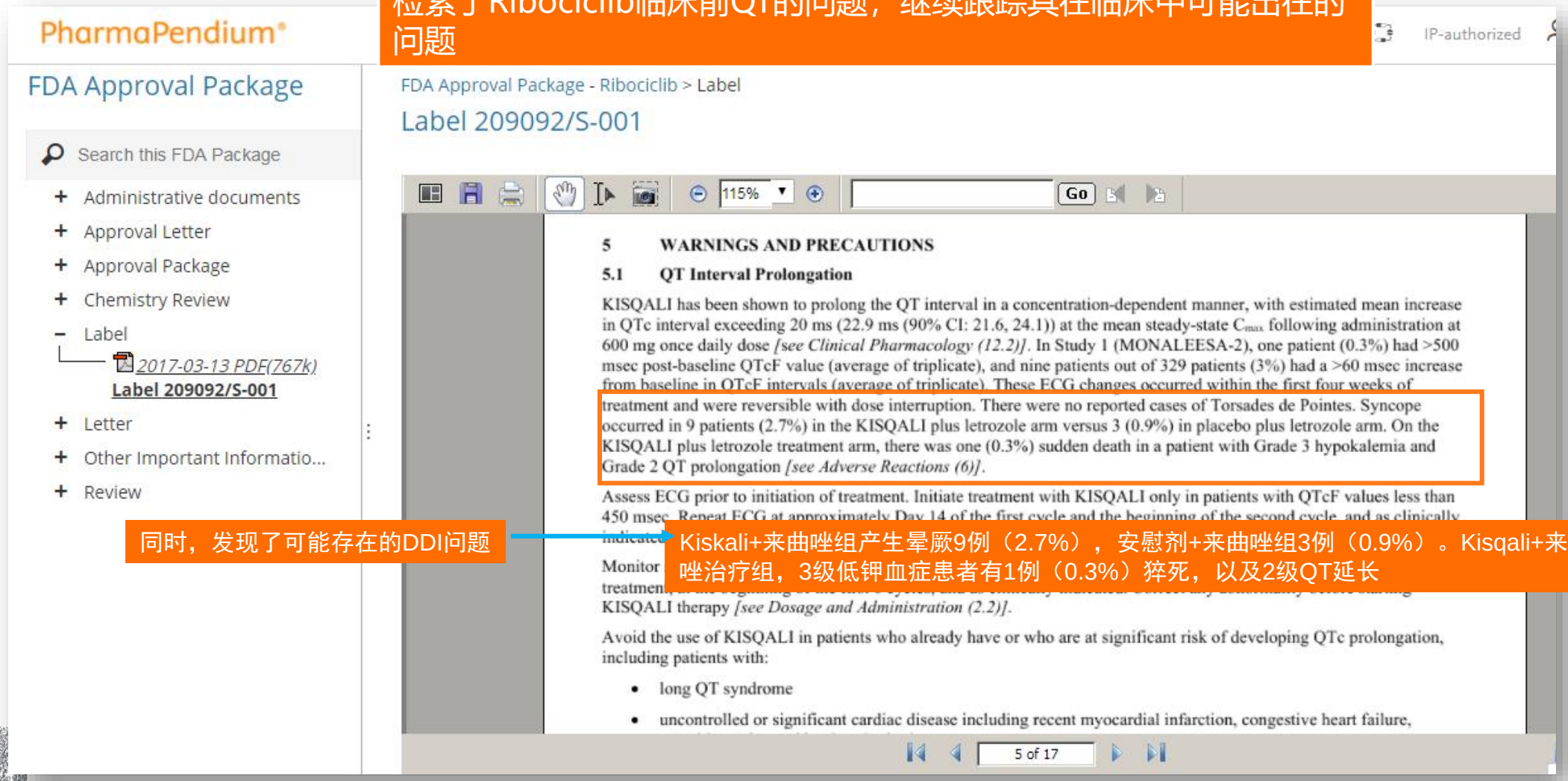
检索了Ribociclib临床前QT的问题，继续跟踪其在临床中可能出在的问题



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

与剂量相关临床QT问题

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

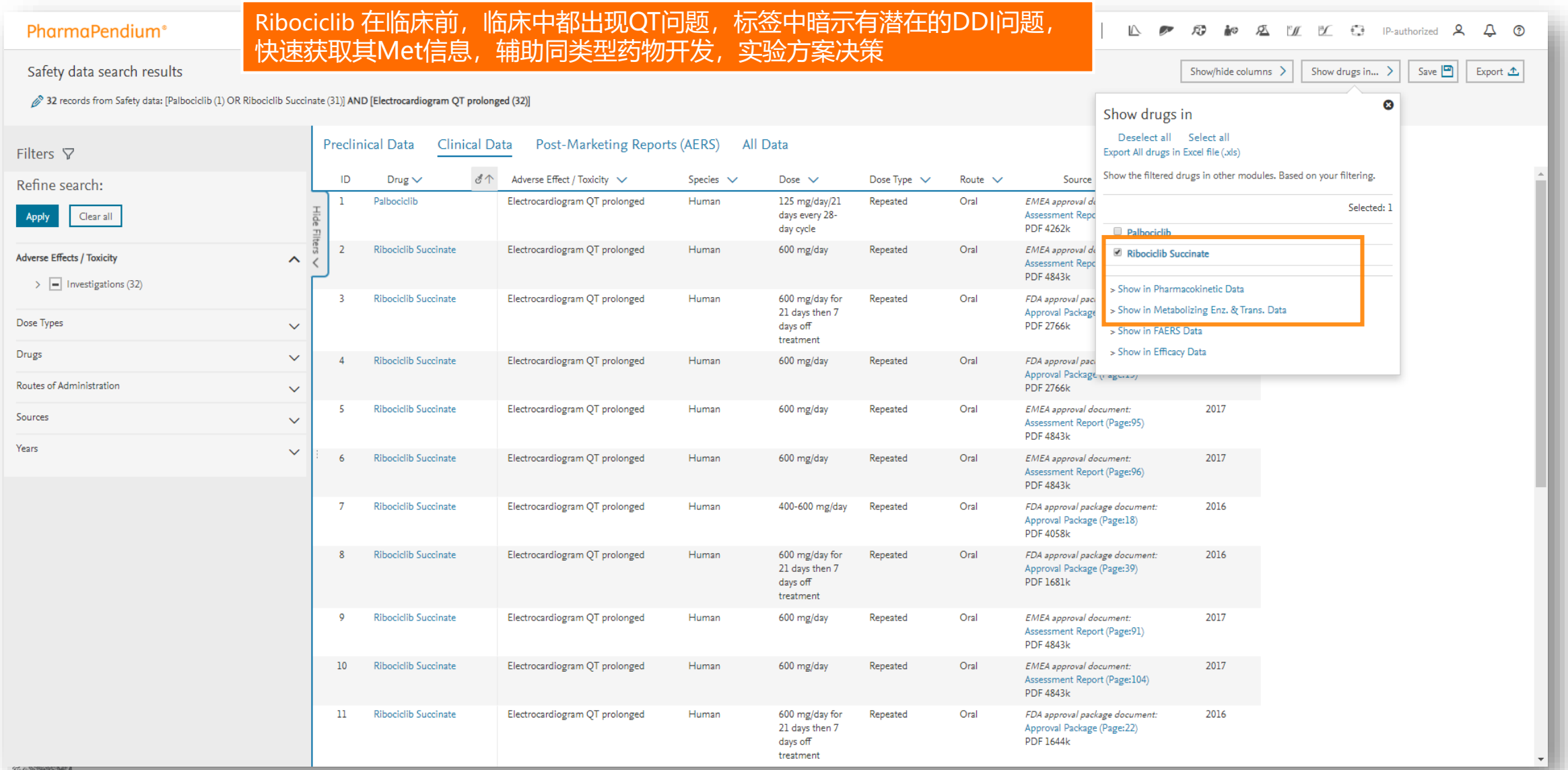


同时，发现了可能存在的DDI问题

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

一键获取特定药物Met信息

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



ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	
1	Palbociclib	Electrocardiogram QT prolonged	Human	125 mg/day/21 days every 28-day cycle	Repeated	Oral	EMEA approval d... Assessment Repo... PDF 4262k	
2	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval d... Assessment Repo... PDF 4843k	
3	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval pac... Approval Package PDF 2766k	
4	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	FDA approval pac... Approval Package PDF 2766k	
5	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:95) PDF 4843k	2017
6	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:96) PDF 4843k	2017
7	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	400-600 mg/day	Repeated	Oral	FDA approval package document: Approval Package (Page:18) PDF 4058k	2016
8	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:39) PDF 1681k	2016
9	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:91) PDF 4843k	2017
10	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day	Repeated	Oral	EMEA approval document: Assessment Report (Page:104) PDF 4843k	2017
11	Ribociclib Succinate	Electrocardiogram QT prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	FDA approval package document: Approval Package (Page:22) PDF 1644k	2016

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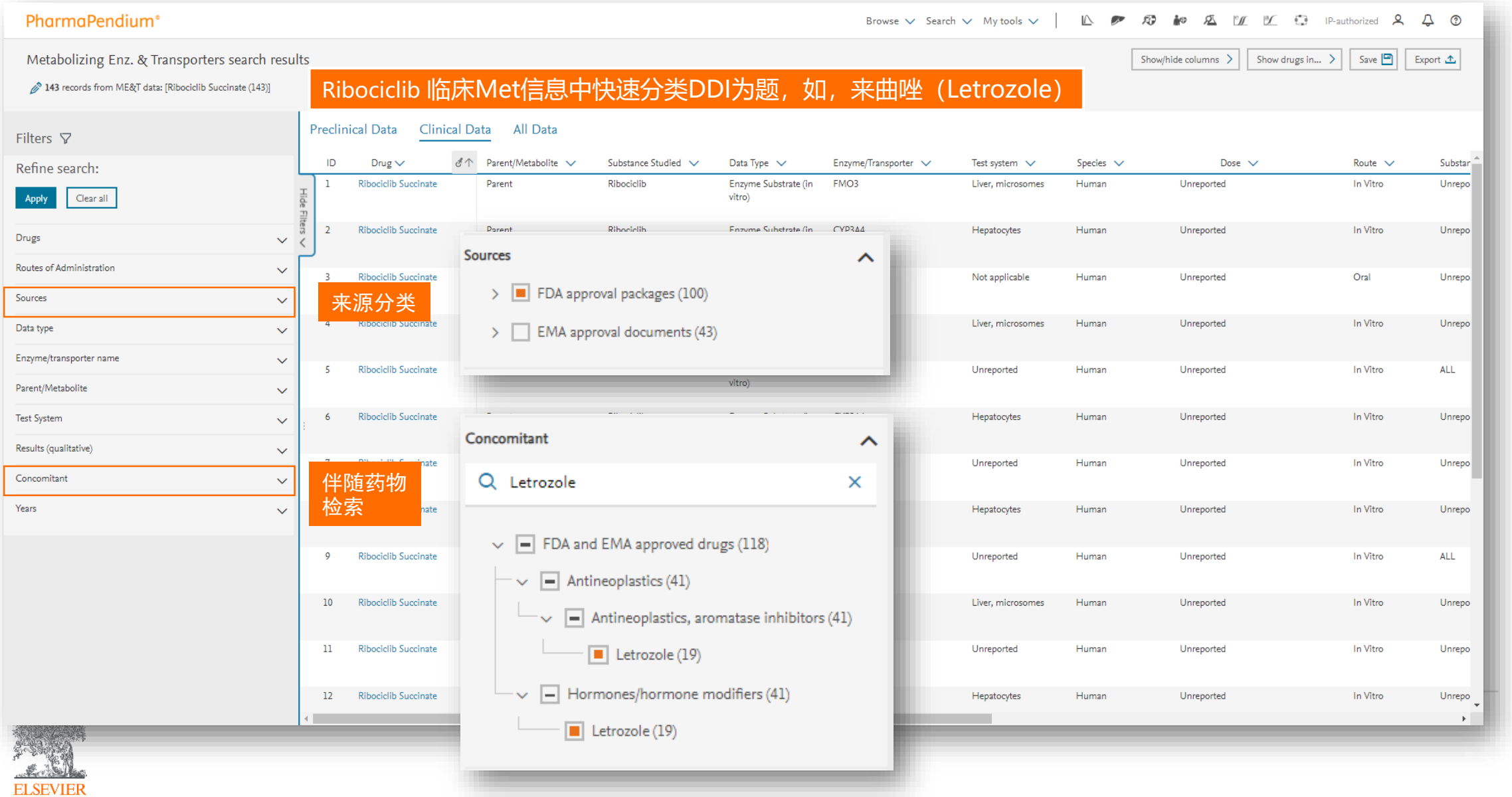
以特定药物Met信息为基础的DDI研究



Letrozole(来曲唑）与Ribociclib的DDI研究

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

伴随药物为来曲唑的，临床研究中所有的PK信息快速获得

Preclinical Data

Show Filters

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

点击查看细节

Letrozole(来曲唑）与Ribociclib的DDI—细节研究

Approval Package 209092/S-000 Part 02

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

DDI between ribociclib and aromatase inhibitors

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

临床研究中显示，来曲唑与Ribociclib不存在DDI问题

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

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

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

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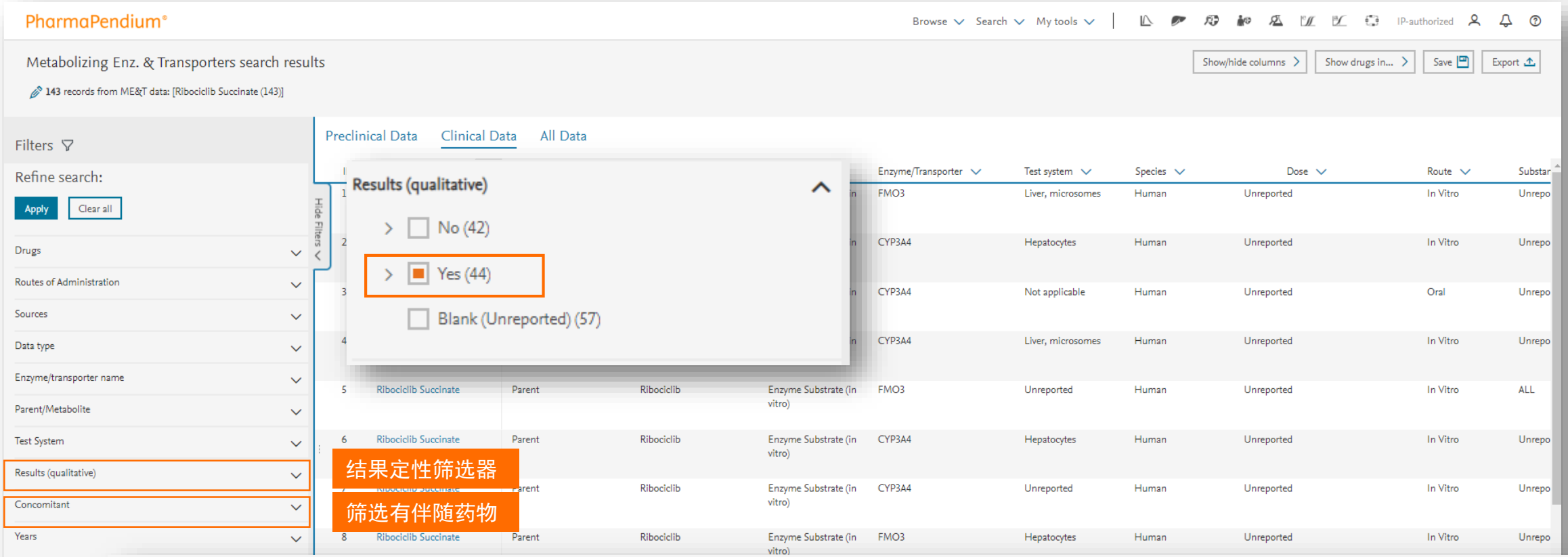
继续探索Ribociclib可能的DDI问题



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继续探索Ribociclib可能的DDI问题—细节

会被Ribociclib影响的药，如midazolam镇静类药物

27%, respectively. A mode… AUC by …
60%, respectively.

Drugs That Are Affected By KISQALI

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

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

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

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

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

In vitro Studies

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

Effect of ribociclib on transporters: In vitro evaluations indicated that KISQALI has a low potential to inhibit the… activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. KISQ… inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

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

同种方法筛选获取的其他细节

000 Part 02

rifampin 1/2 Go

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

clearance is predicte… n (See
Section 13.3.5.4 for … th
ritonavir provided a… stration
without a CPY3A inh… t use of
a strong CYP3A4 inh… d.

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

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

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

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

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

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

今天的内容

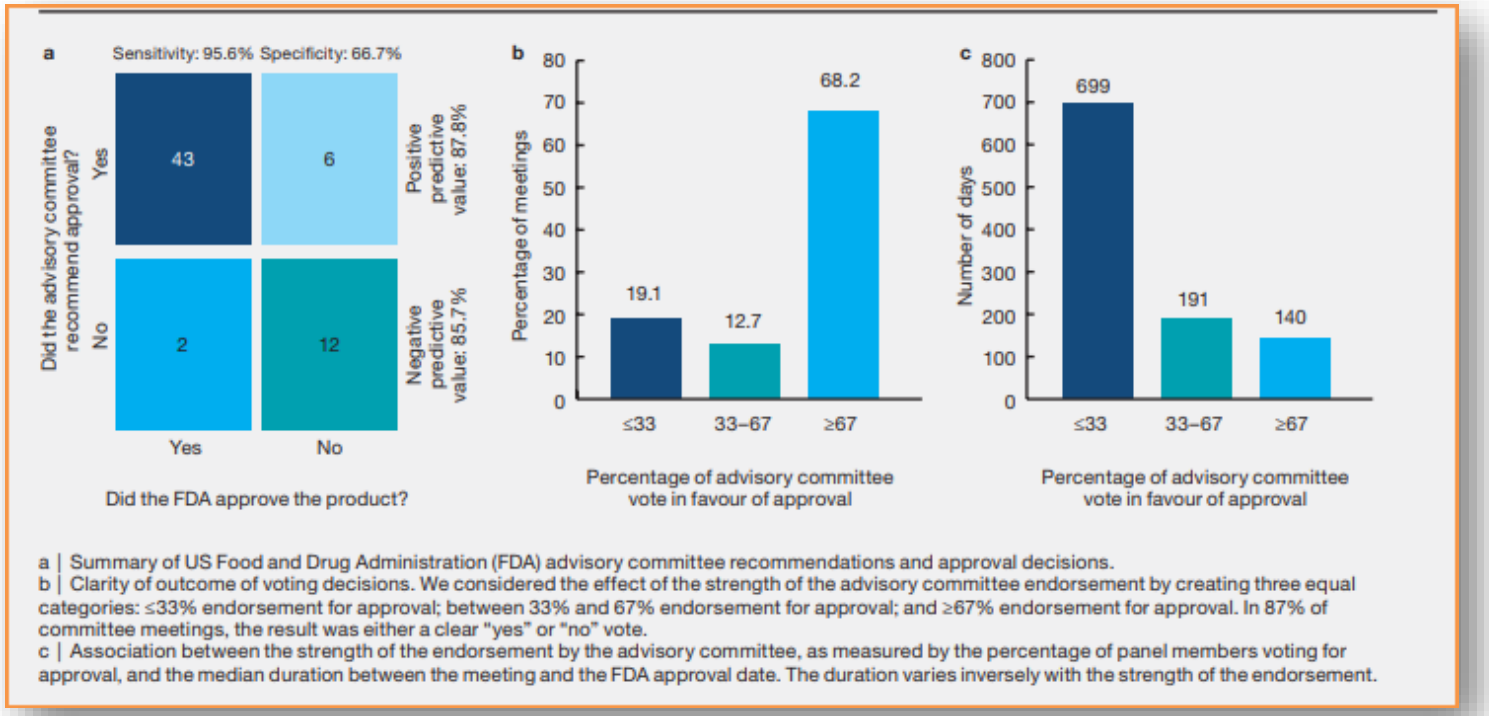
- ParmaPendium数据库的简介
  - PharmaPendium中的内容
  - PharmaPendium中的检索模块与基本应用
- ParmaPendium数据库的应用
  - 涉及药物的安全性、药效、DMPK数据获取的应用
    - 单一/一类药物数据的获取
    - 涉及特殊安全性研究（QT延长毒性）的相关报道的获取
  - 涉及新药申请方面的应用
    - 如何为非验证性“替代临床终点”提供证据支持
    - 如何为因“种族差异”导致的剂量差别寻找证据支持
  - Met代谢数据检索及DDI预测的应用
    - 抗肿瘤药物的代谢酶或转运体活性显著变化的信息检索
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

涉及新药申请方面的应用

Case 3：如何为“非验证替代临床终点”提供证据支持
Case 4：如何为因“种族差异”导致的剂量差别寻找证据支持

FDA 评审委员会会议档案检索的重要性

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

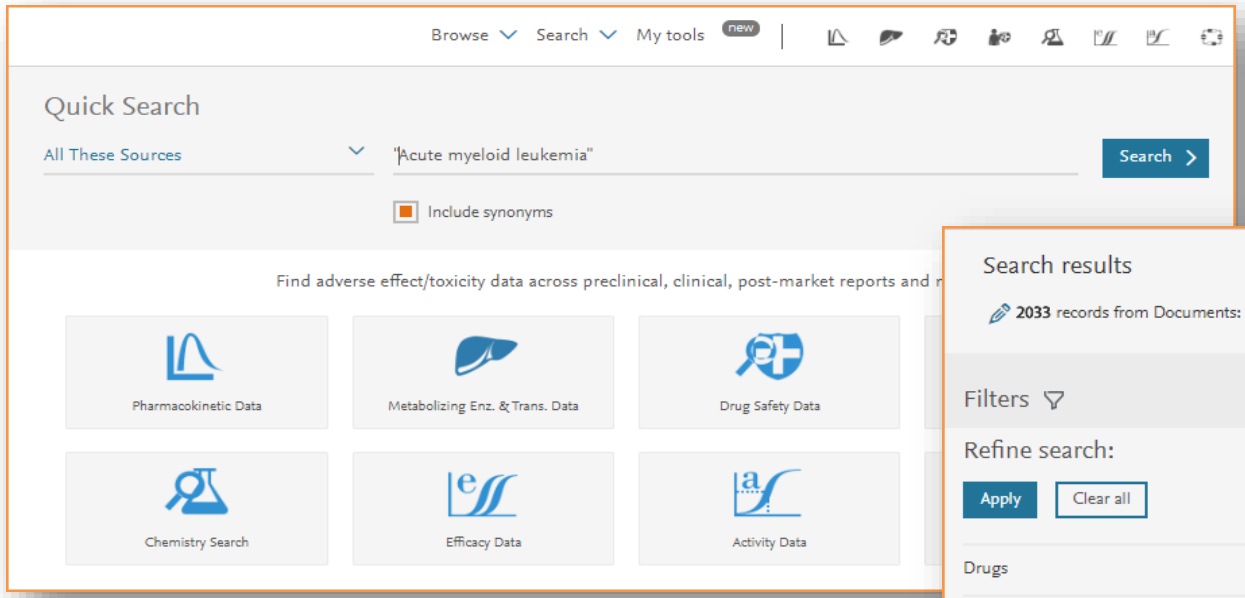


a | Summary of US Food and Drug Administration (FDA) advisory committee recommendations and approval decisions.
b | Clarity of outcome of voting decisions. We considered the effect of the strength of the advisory committee endorsement by creating three equal categories: ≤33% endorsement for approval; 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.

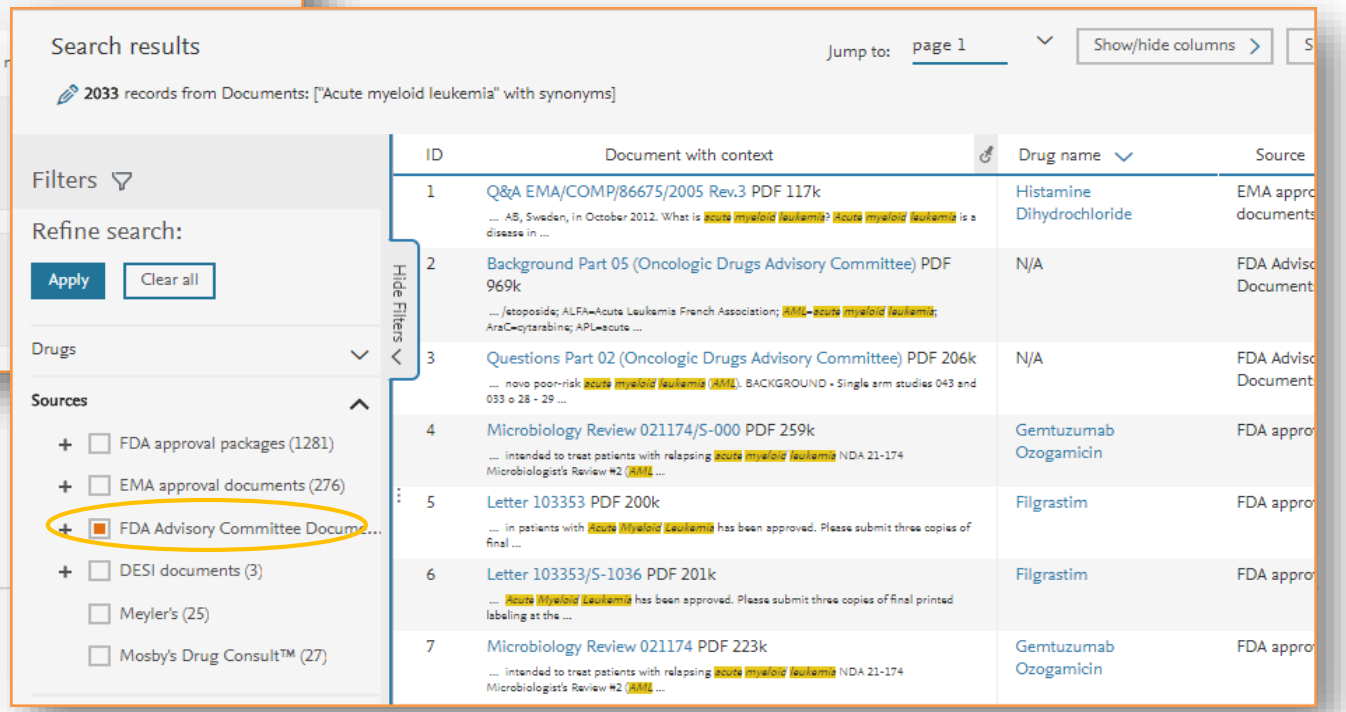
https://www.mckinsey.com/~/media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx

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



“Acute myeloid leukemia” 进行free text检索



结果集中，筛选 ‘sources’ 的中的AC报告

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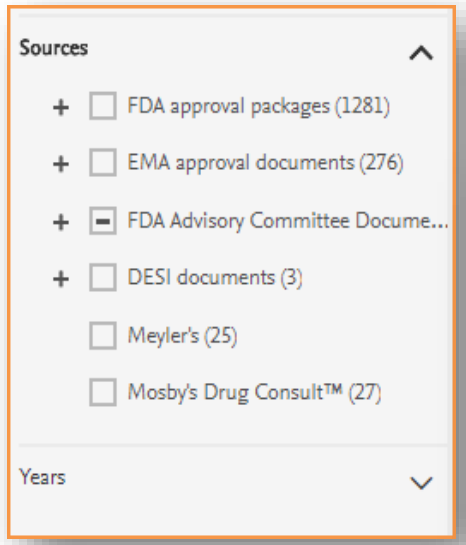
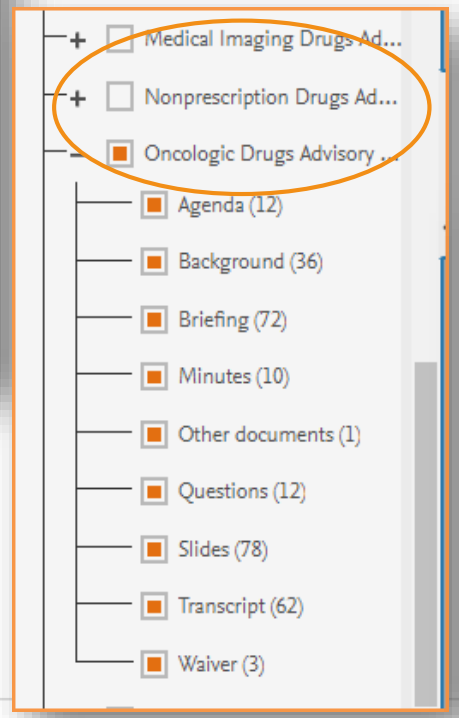
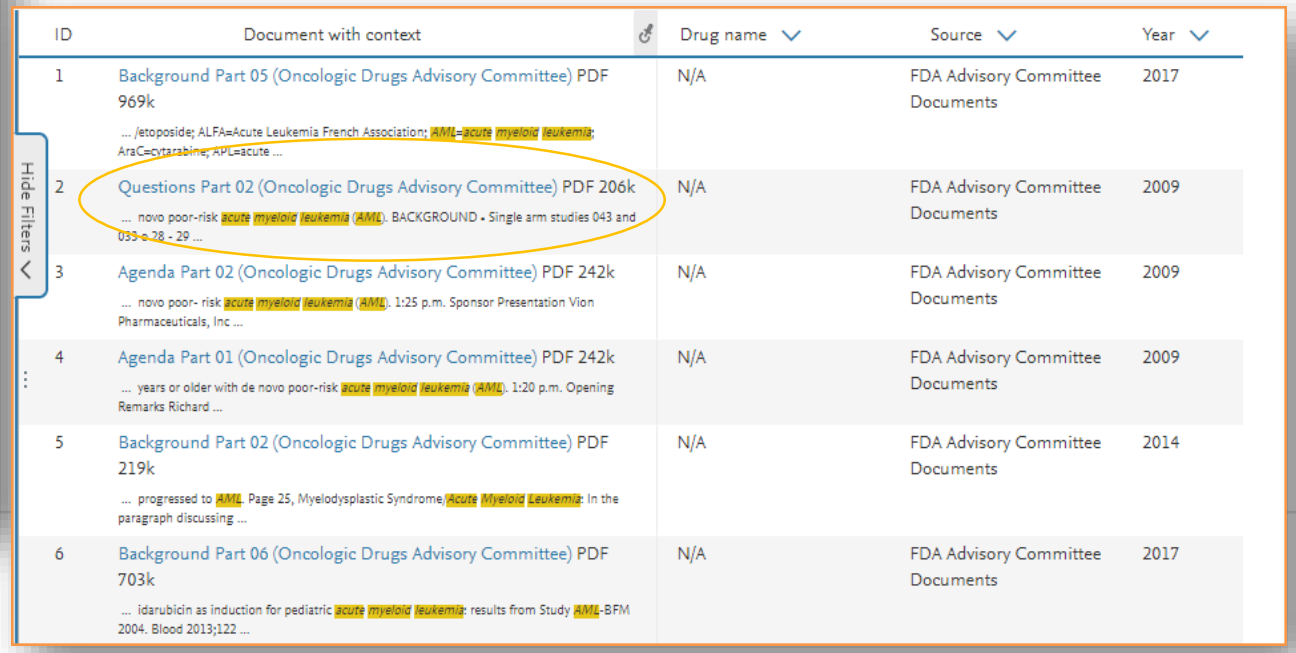
FDA-AC-快速分类不同评审的结果

进一步分类用于治疗AML（急性髓细胞白血病）相关肿瘤药物AC 报告





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



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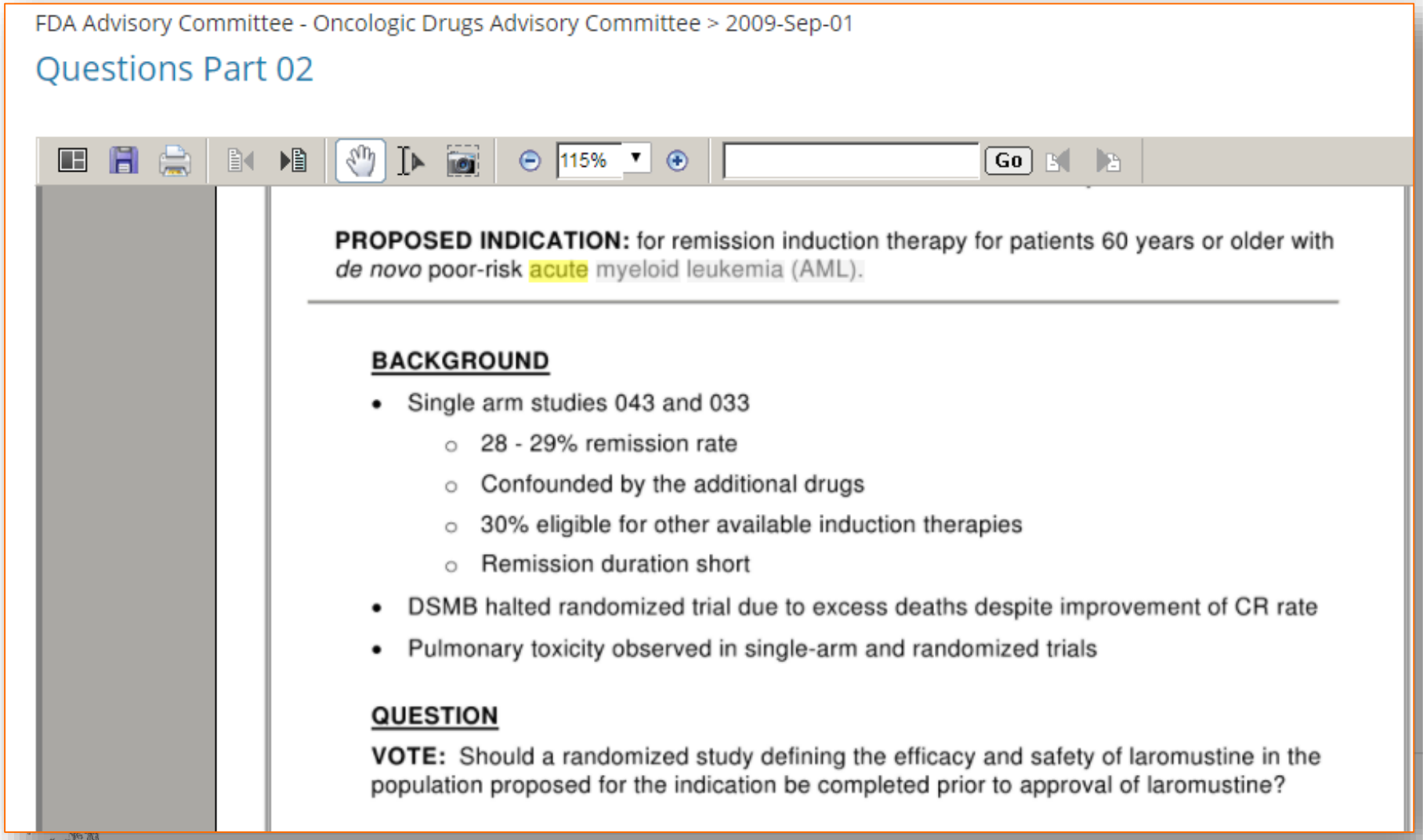
FDA-AC---评审委员会评审意见细节



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

Questions Part 02

115% Go

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

BACKGROUND

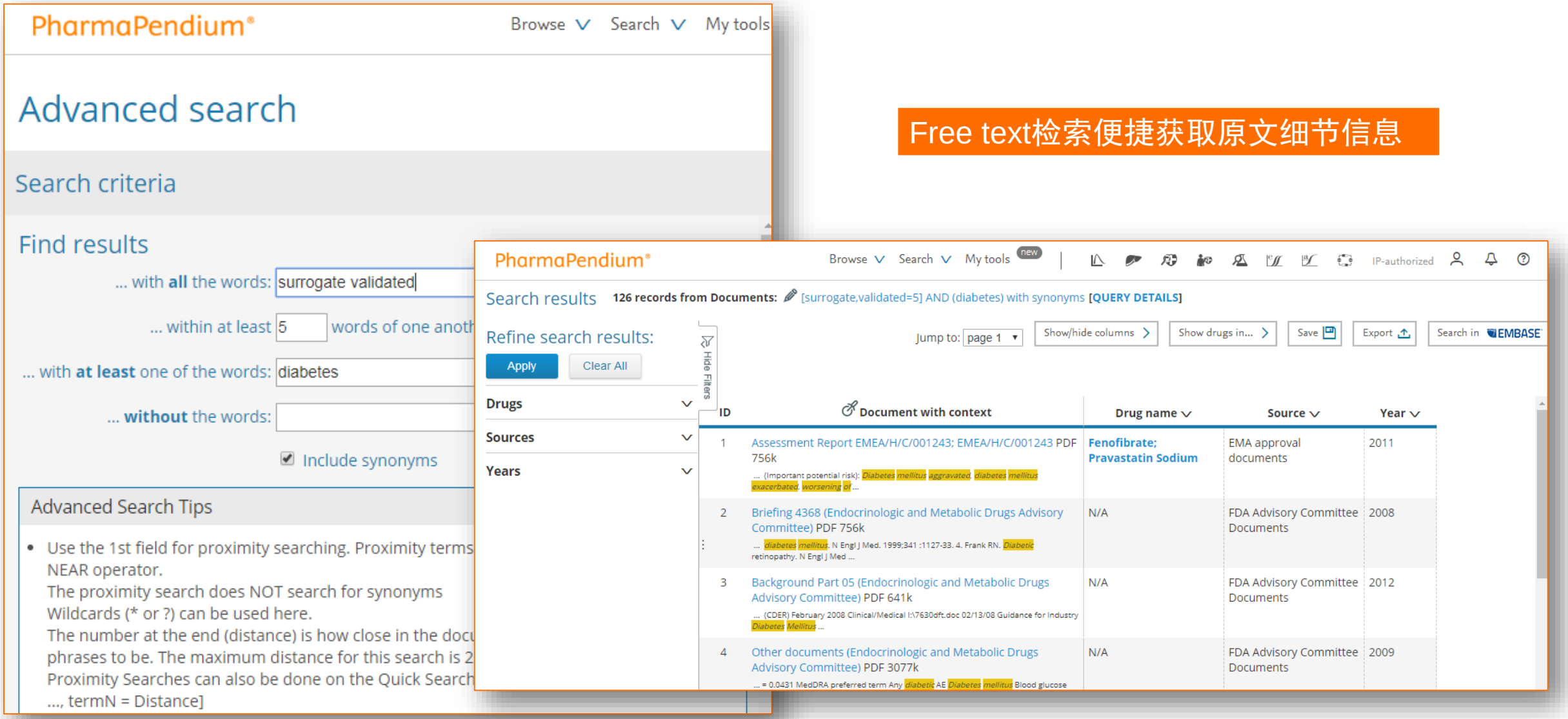
- Single arm studies 043 and 033
  - 28 - 29% remission rate
  - Confounded by the additional drugs
  - 30% eligible for other available induction therapies
  - Remission duration short
- DSMB halted randomized trial due to excess deaths despite improvement of CR rate
- Pulmonary toxicity observed in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

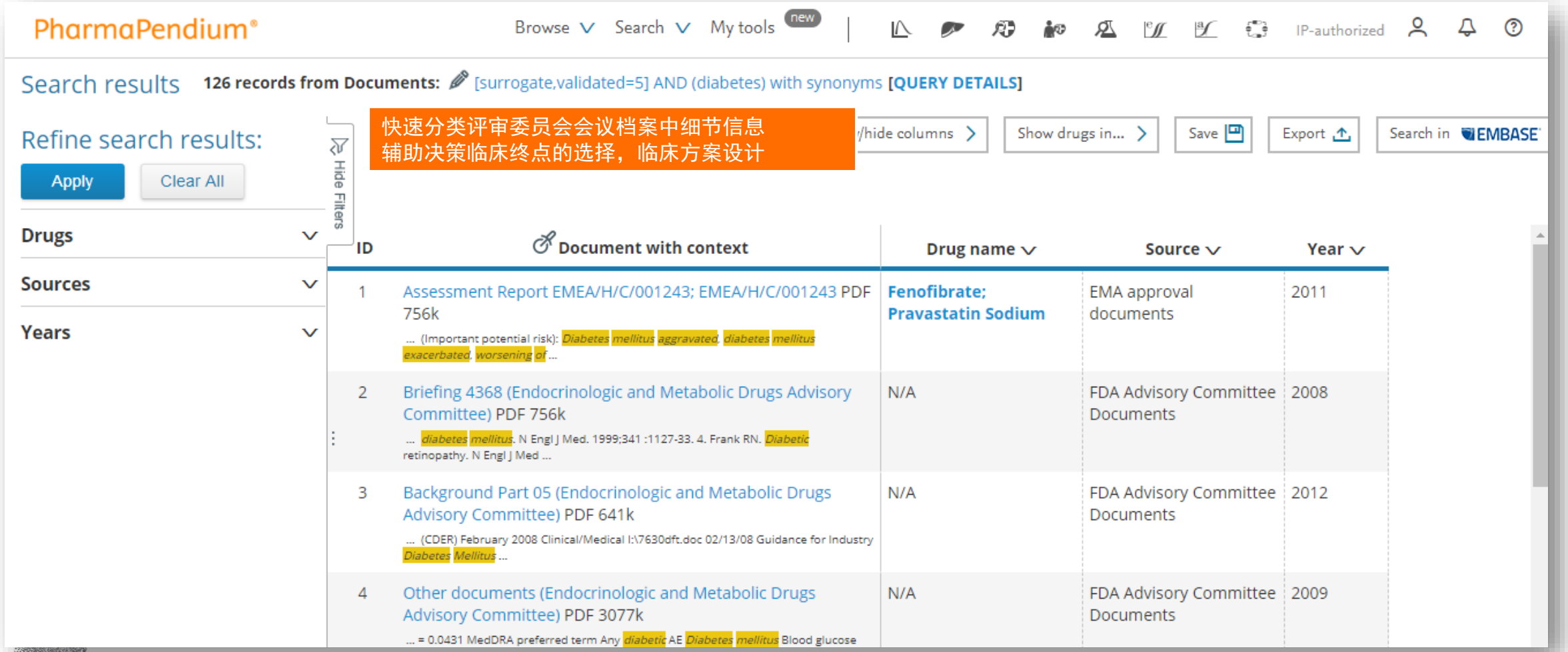
随机对照组实验,能够验证laromustine在前期递交申请中的提到的对相应目标人群适应症的治疗药效和安全性吗?

Case 3:如何为糖尿病“替代临床终点”提供证据支持



Free text检索便捷获取原文细节信息

获得FDA 评审委员会对于临床终点的各种信息



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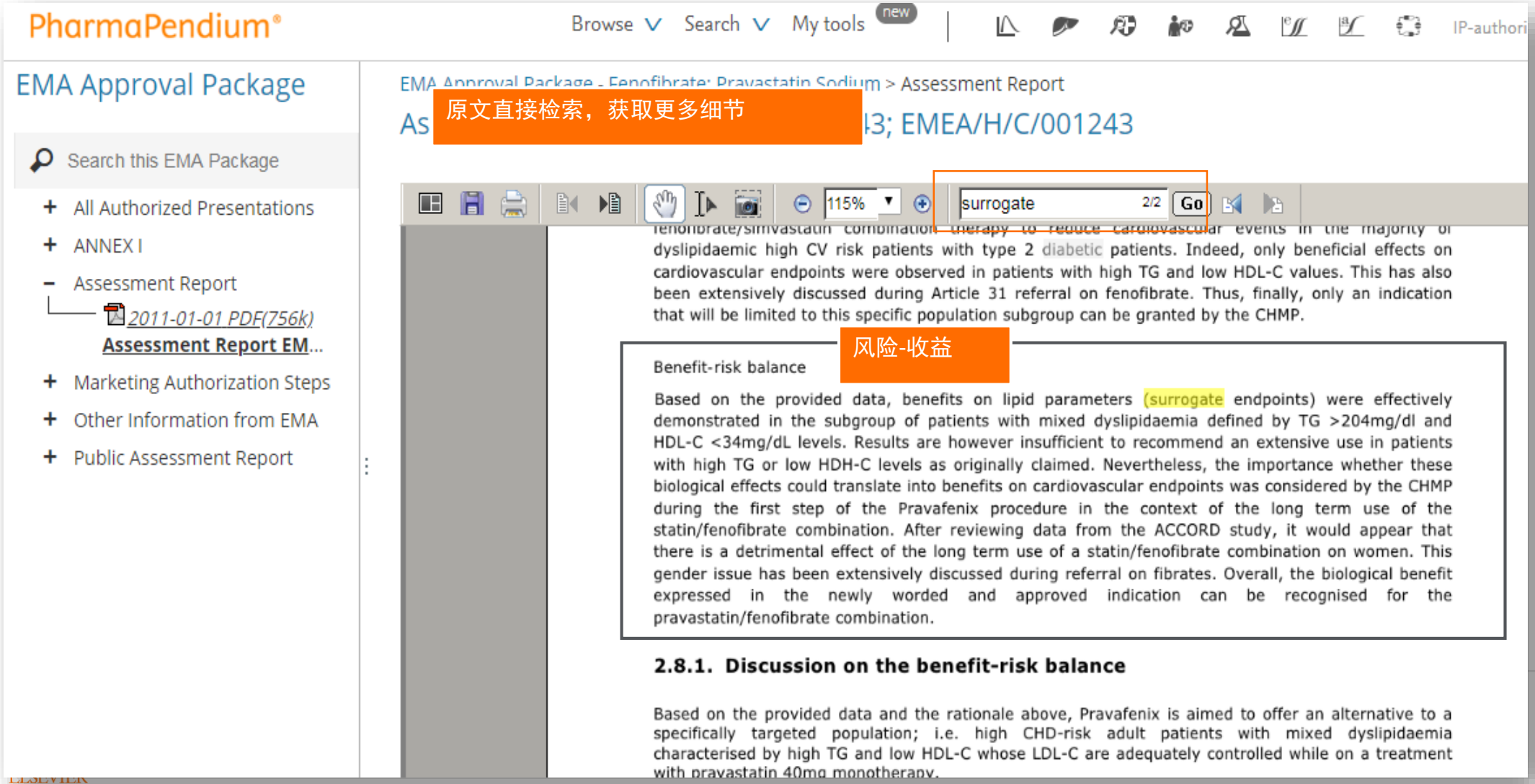
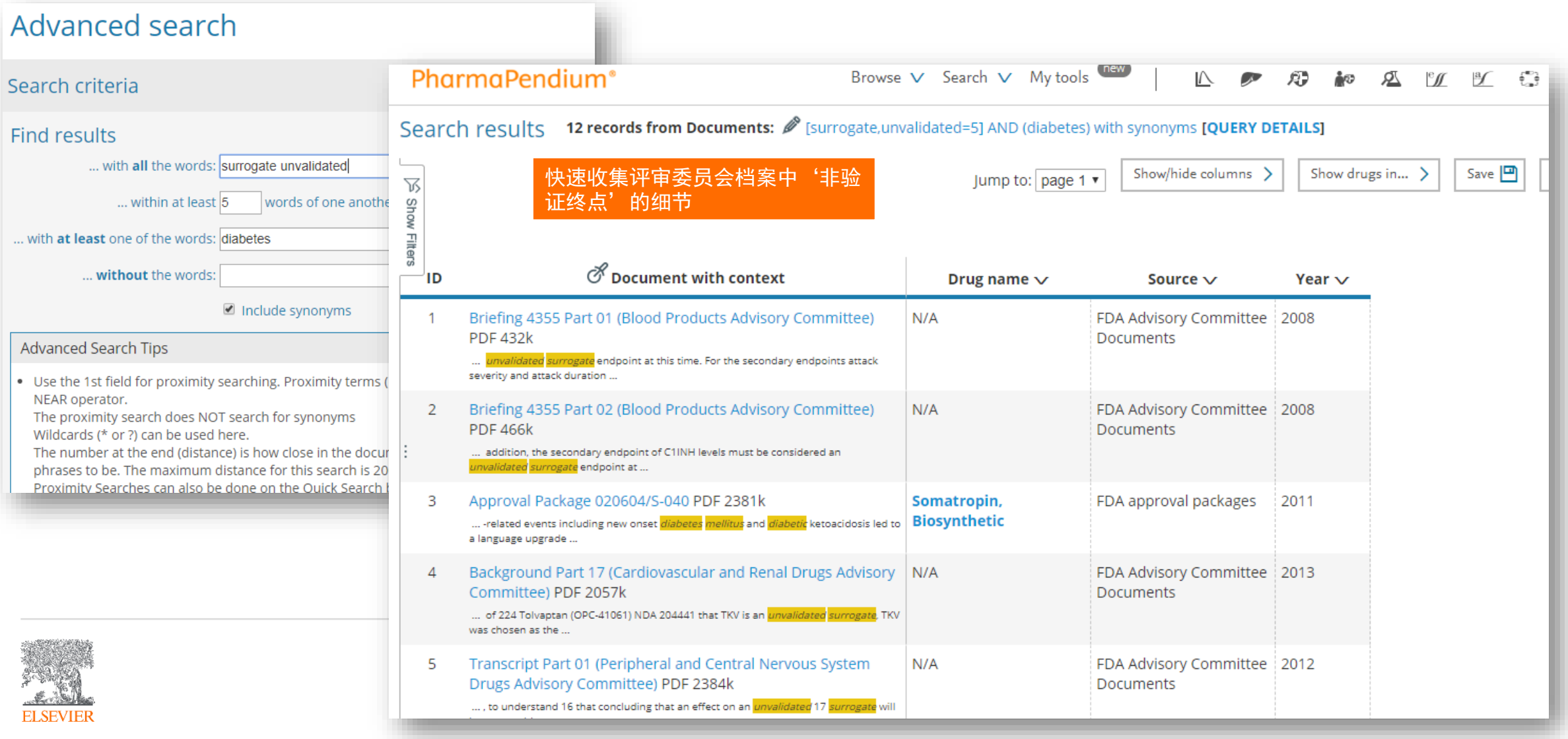
快速获取特定原文中的临床终点信息



“非验证替代终点”原文信息的检索



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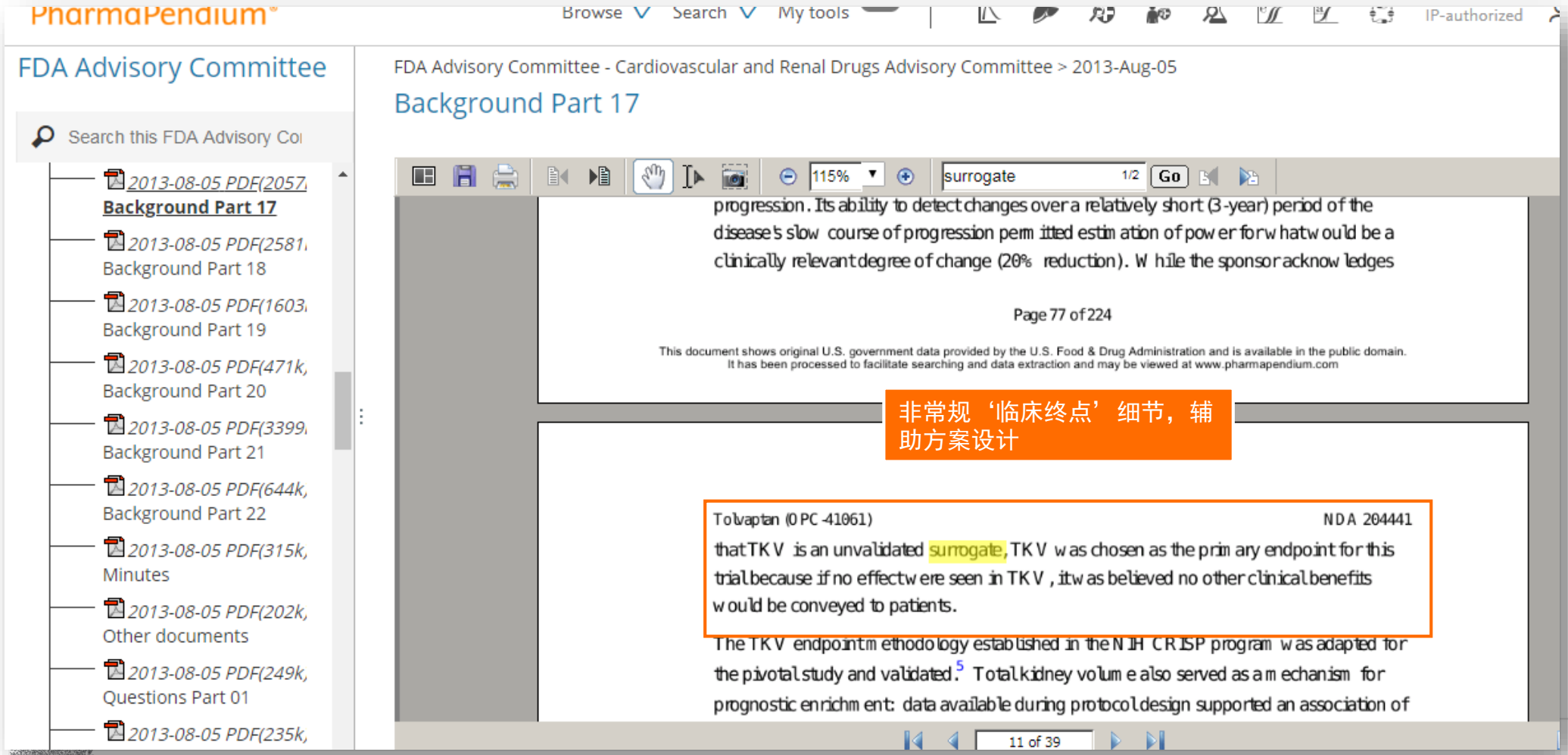
获取原文中的细节描述



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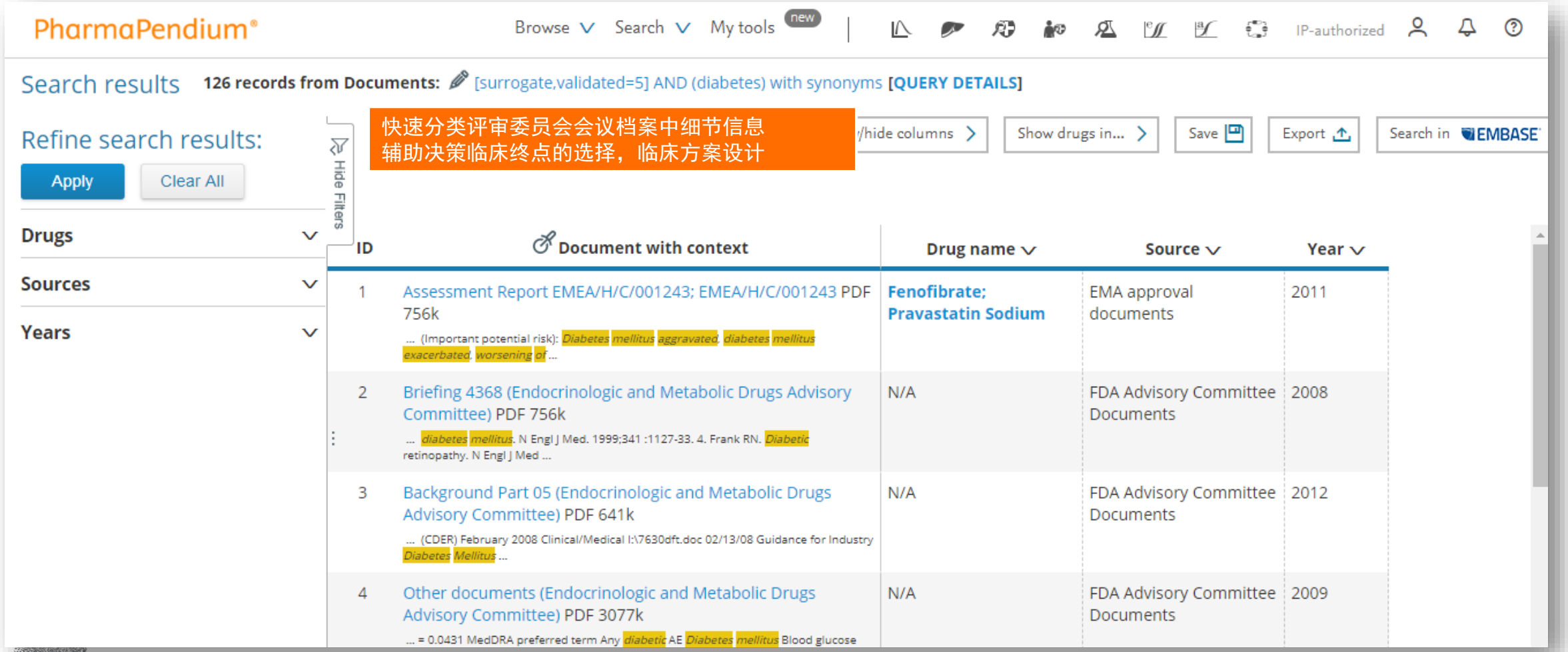
获得FDA 评审委员会对于临床终点的各种信息



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Case 4:如何为因“种族差异”导致的针对不同种族的剂量差别寻找证据支持

内在和外在的因素会影响PK/PD

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

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

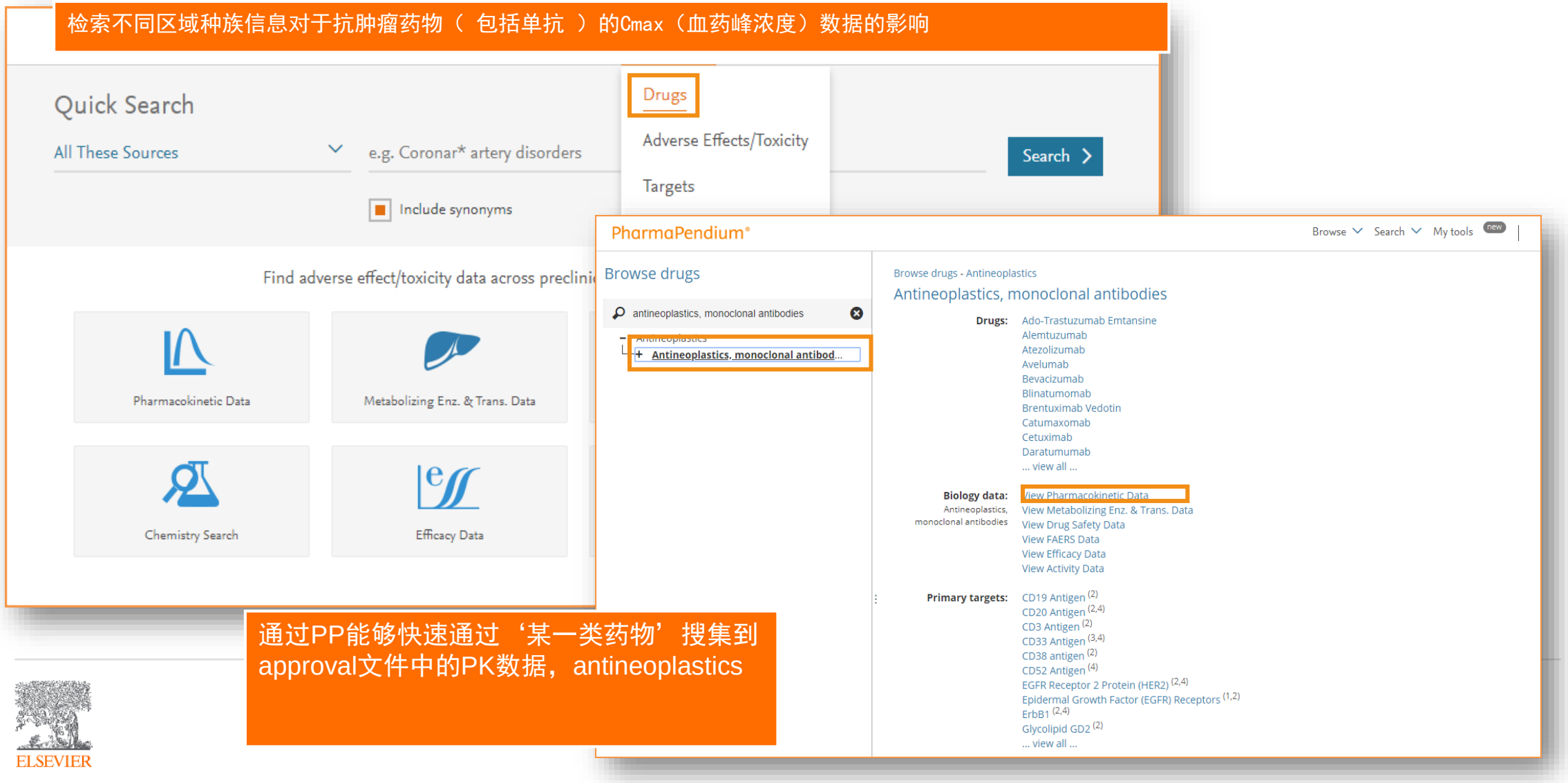
在FDA的知道文件当中注明，种族因素是一个影响药效和安全的重要因素，因此在设计临床实验，以及IND, NDA申请的时候需要考虑这些因素对在研药物的影响，**那么快速高效的收集相关信息，有助于决策**

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，antineoplastics

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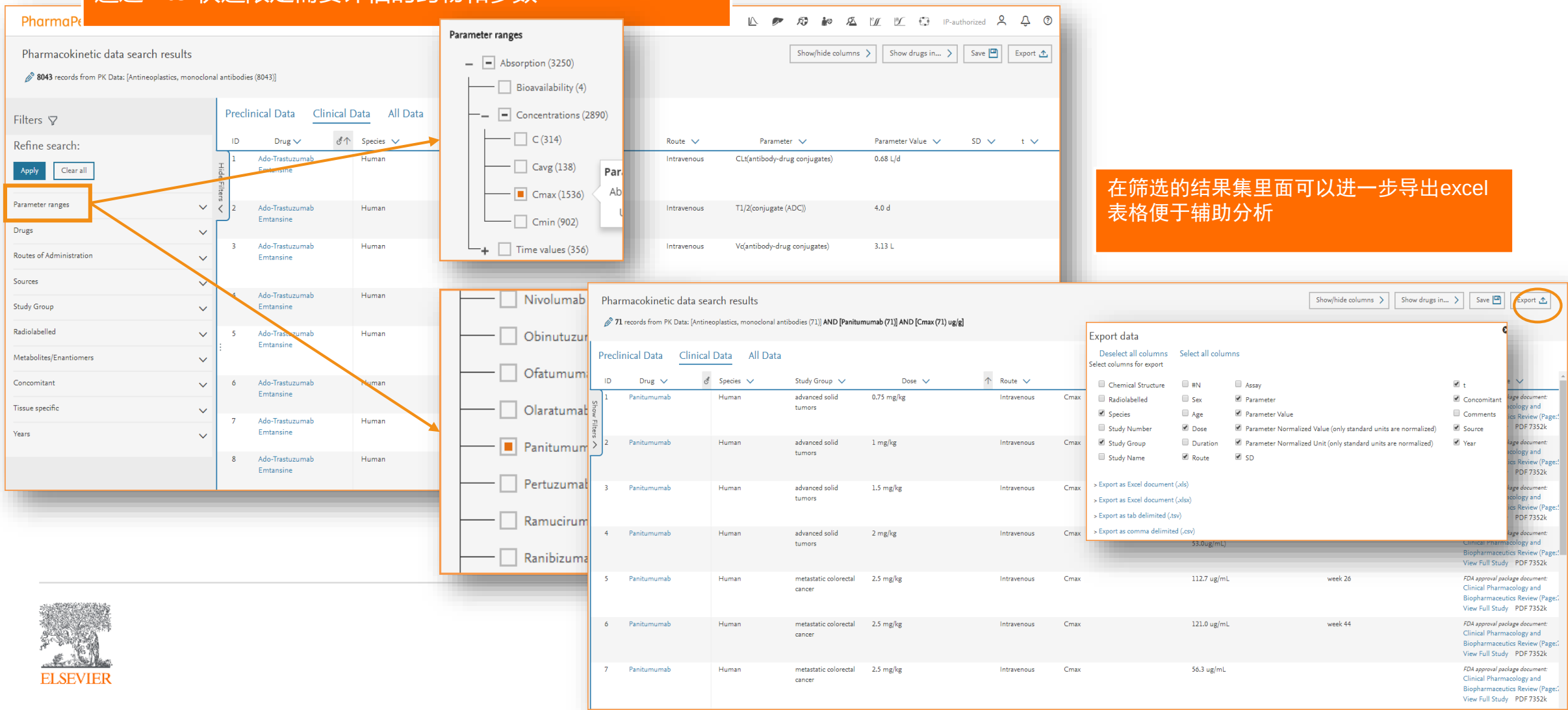
Pharmacokinetic---参数的快速限定

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

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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	Intravenous					
Panitumumab	Human	Japanese with advanced solid tumors	2.5 mg/kg	Intravenous					
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous					
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous					
Panitumumab	Human	metastatic colorectal cancer	2.5 mg/kg	Intravenous					
Panitumumab	Human	Japanese with advanced solid tumors	2.5 mg/kg	Intravenous					
Panitumumab	Human		2.5 mg/kg	Intravenous					
Panitumumab	Human	renal carcinoma	2.5 mg/kg/wk	Intravenous					
Panitumumab	Human	advanced solid tumors	3.5 mg/kg	Intravenous					
Panitumumab	Human	advanced solid tumors	5 mg/kg	Intravenous					
Panitumumab	Human	colorectal cancer, various other solid tumour	6 mg/kg	Intravenous					
Panitumumab	Human	metastatic colorectal cancer	6 mg/kg	Intravenous					
Panitumumab	Human	advanced solid tumors	6 mg/kg	Intravenous					
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg	Intravenous					
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg	Intravenous					
Panitumumab	Human		6 mg/kg	Intravenous					
Panitumumab	Human		6 mg/kg	Intravenous					
Panitumumab	Human	advanced solid tumors	6 mg/kg	Intravenous					
Panitumumab	Human	advanced solid tumors	6 mg/kg	Intravenous					
Panitumumab	Human		6 mg/kg	Intravenous					
Panitumumab	Human	Japanese with advanced solid tumors	6 mg/kg	Intravenous					
Panitumumab	Human	solid tumours that had proven refractory to c	6 mg/kg	Intravenous					
Panitumumab	Human		6 mg/kg	Intravenous					
Panitumumab	Human		6 mg/kg	Intravenous					

	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/#/brow	
8	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
9	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
10	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
11	ug/mL		week 26		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
12	ug/mL		week 44		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
13	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
14	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
15	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
16	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
17	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
18	ug/mL		week 17		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
19	ug/mL		week 8		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
20	ug/mL		week 35		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
21	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
22	ug/mL	35.0			EMA approval document: Scientific Discussion, page:15 PDF 506k	https://www.pharmapendium.com/#/brow	2007
23	ug/mL	38.0	week 23		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
24	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
25	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
26	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brow	2007
27	ug/mL	24.6	week 23		FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
28	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
29	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brow	2007
30	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brow	2007
31	ug/mL	59.0			EMA approval document: ANNEX I, page:16 PDF 477k	https://www.pharmapendium.com/#/brow	
32	ug/mL	59.0			FDA approval package document: Label 125147/S-0067, page:10 PDF 5	https://www.pharmapendium.com/#/brow	2009
33	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
34	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
35	ug/mL	59.0			FDA approval package document: Printed Labeling 125147/S-0000, pag	https://www.pharmapendium.com/#/brow	2006
36	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	03df0e07b424c6?reference=54	
37	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brow	2007
38	ug/mL		after the third dose		FDA approval package document: Administrative documents 125147/S-	https://www.pharmapendium.com/#/brow	2006
39	ug/mL	59.0			FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
40	ug/mL				FDA approval package document: Clinical Pharmacology and Biopharma	https://www.pharmapendium.com/#/brow	
41	ug/mL				EMA approval document: Scientific Discussion, page:17 PDF 506k	https://www.pharmapendium.com/#/brow	2007
42	ug/mL		after the third dose		FDA approval package document: Administrative documents 125147/S-	https://www.pharmapendium.com/#/brow	2006
43	ug/mL	59.0			FDA approval package document: Label 125147/S-0000, page:2 PDF 13	https://www.pharmapendium.com/#/brow	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

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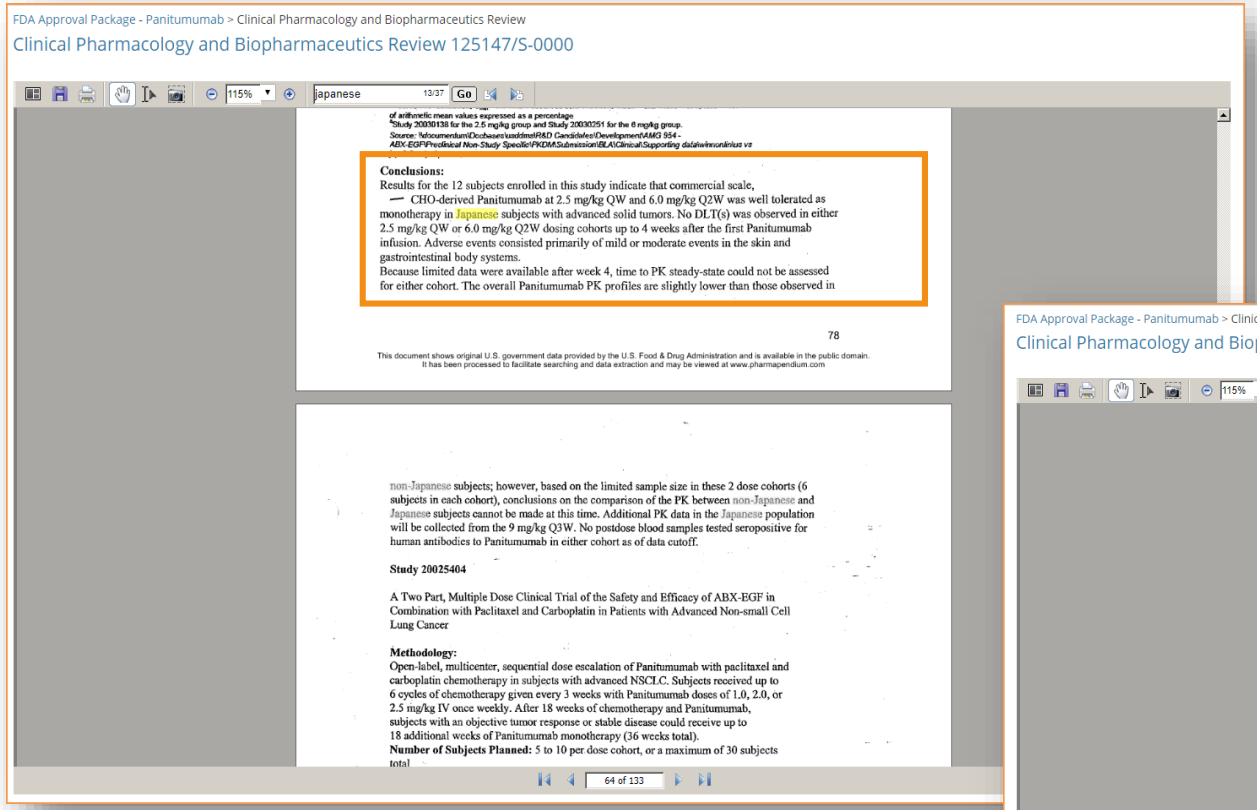
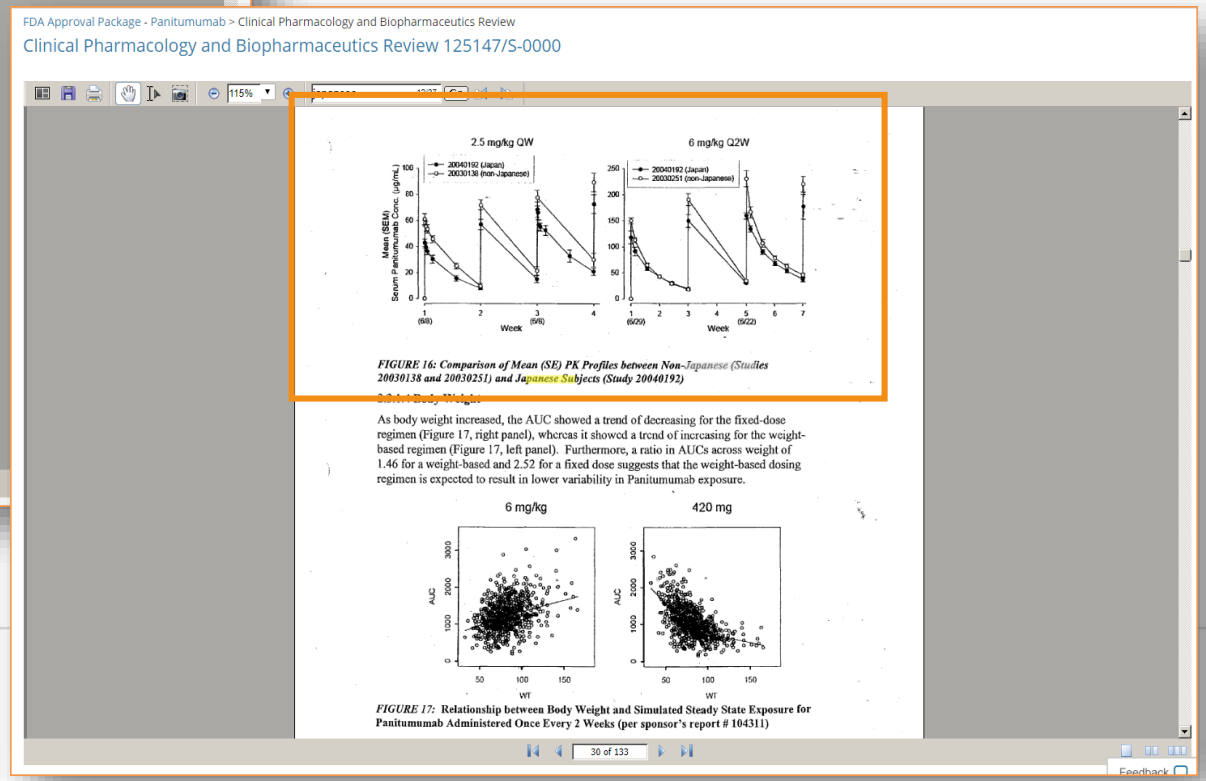
Pharmacokinetic---原始文献查看



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



Met代谢数据检索及DDI预测的应用

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

药物相互作用的早期和持续评估至关重要

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

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

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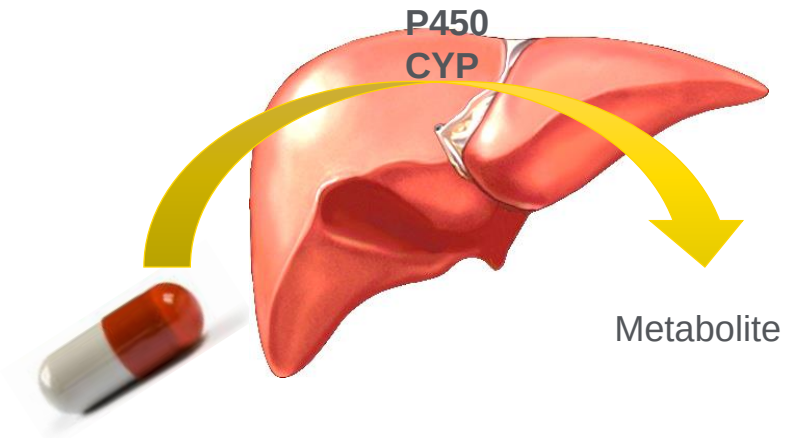
[1] Guthrie et al. BMC Medicine (2015) 13:74

药物-药物相互作用可增加毒性或降低临床疗效。

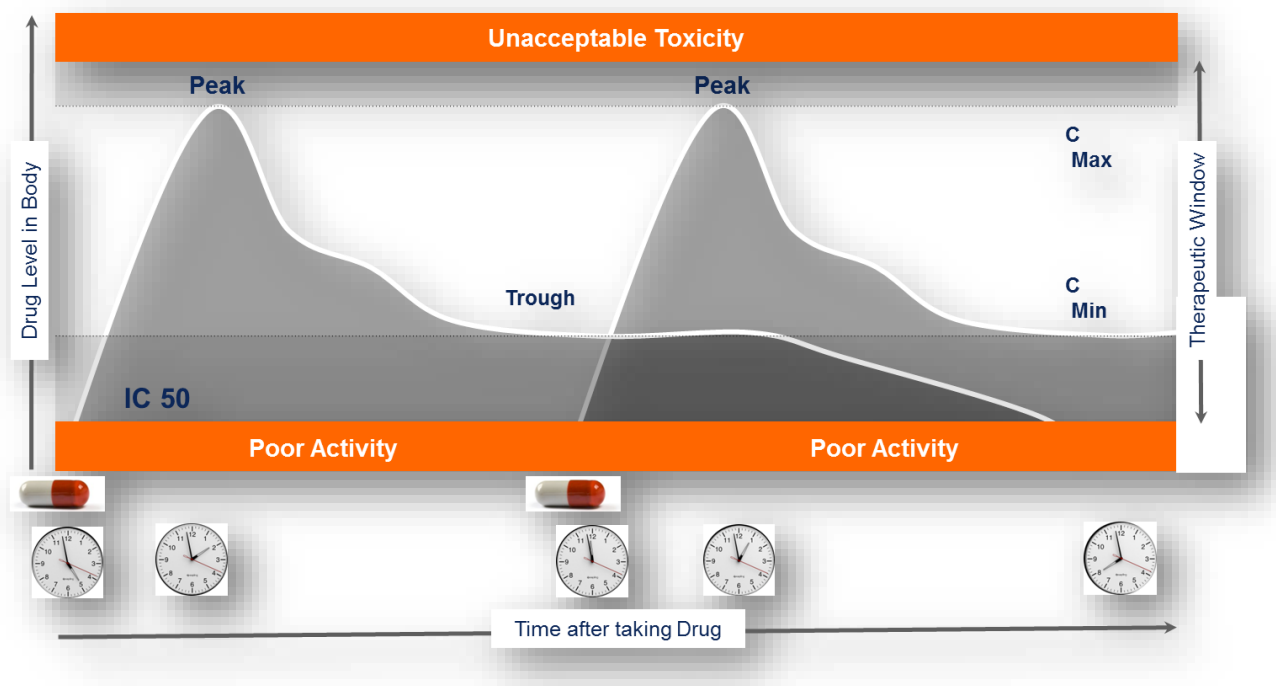
由AUC（曲线下面积）测量，增加/减少

药物代谢的主要机制（约占75%）是通过肝脏中的p450 CYP酶。



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

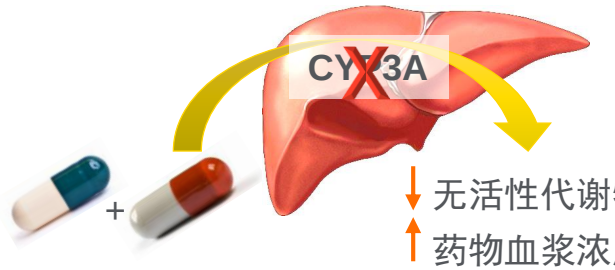
伴随用药=同时服用两种或两种以上的药物

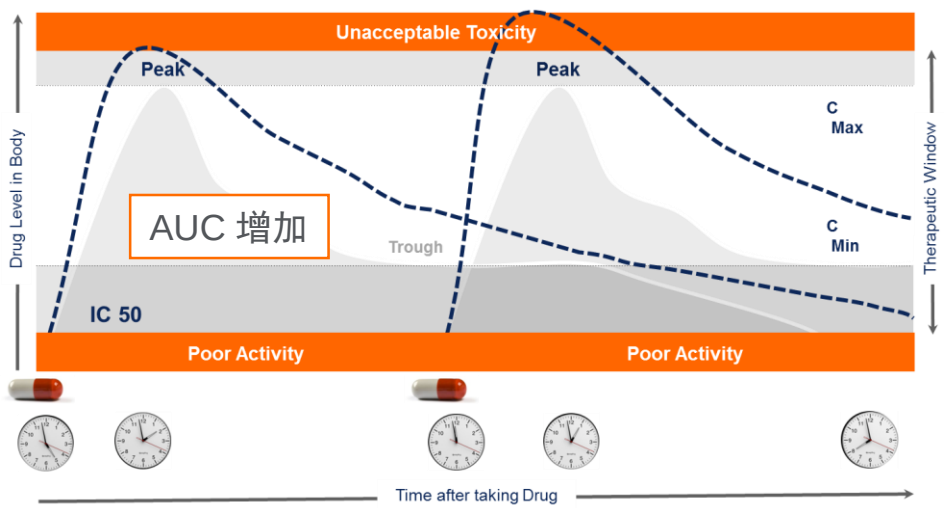


如，药物A口服，由CYP3A代谢

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

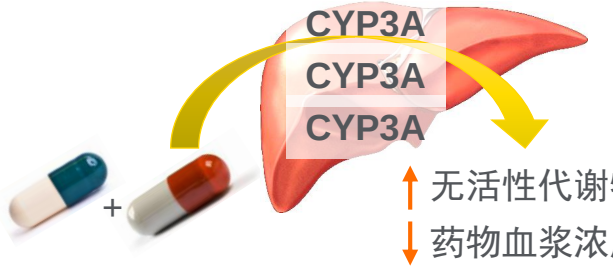
伴随药物抑制CYP酶的代谢

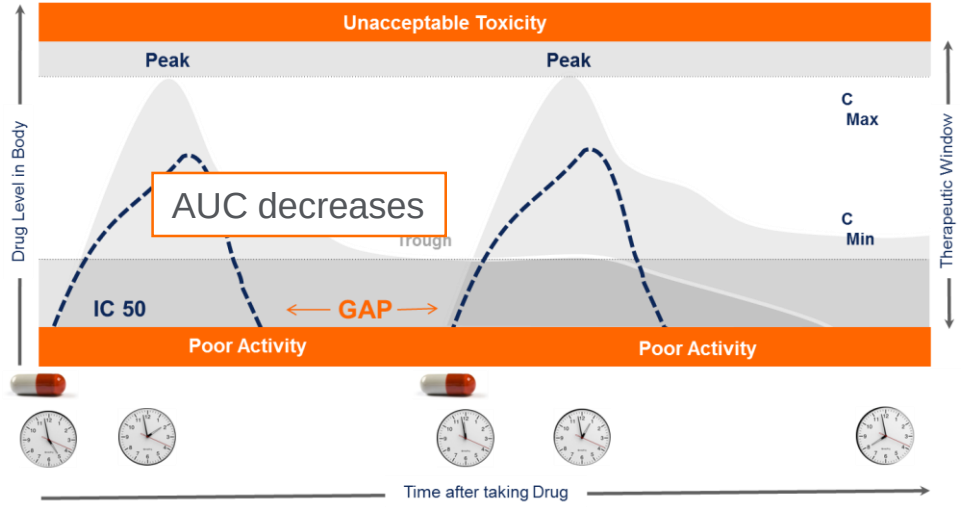




如,药物A由cyp3A代谢，药物B抑制cyp3A的活性，药物A不再以相同的速率代谢，导致毒性浓度的累积

伴随药物诱导CYP酶的代谢



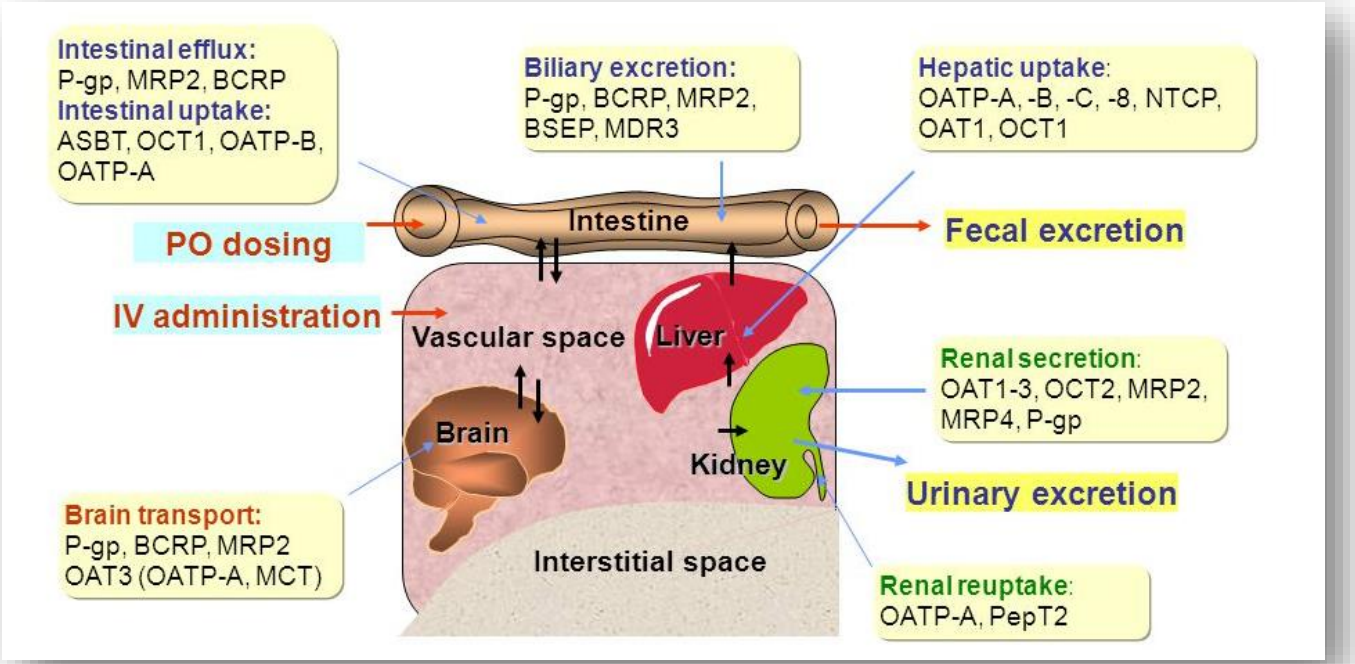


如,药物A由cyp3A代谢，药物B诱导cyp3A的活性，药物A不再以相同的速率代谢，导致浓度降低，疗效下降.

DDI也通过联合用药抑制或诱导药物转运体发生

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

➢ DMPK模块包含代谢酶和转运蛋白的综合信息



Boehringer Ingelheim http://slideplayer.com/slide/5810493/

DMPK 模块

为候选药物潜在的风险提供更完整的评估，辅助决策。

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

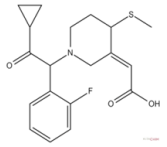
DDI 风险预测计算器(DDIRC)

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

MET+PK参数直接定位对应信息

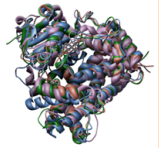
Metabolites

Created, when available

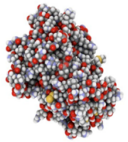


CYPs

Either involved in the metabolism or up/down regulated by the drug, quantitative and qualitative data

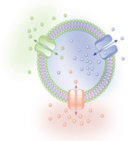


Phase 2 Enzymes



Transporters

And drug effects on transporters

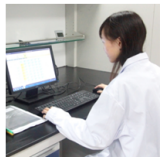


In Vitro

***Dynamic* parameters** such as CLint (Intrinsic Clearance) and Km (Michaelis Constant), Vmax (Maximum rate of reaction)

DDI Studies

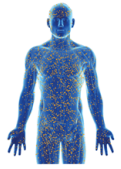
Ratio of AUC, Clearance, etc. in presence of another drug.



药物在检索时被分为: 底物, 诱导剂和抑制剂

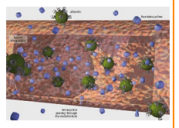
Absorption

Includes:
- % Absorbed
- Bioavailability
- Concentrations
- Fraction absorbed
- Time values



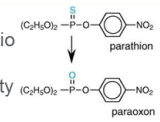
Binding

Includes:
- Cell binding
- Protein binding



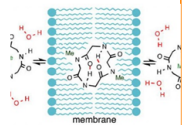
Biotransformation

Includes:
- Enantiomeric ratio
- Metabolic ratio
- Metabolic stability
- Metabolic transformation



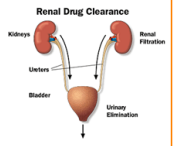
Distribution

Includes:
- Accumulation
- AUC
- Permeation
- Steady state
- Time value
- Tissue distribution
- Volume of distribution



Elimination

Includes:
- Clearance
- Excretion values
- Half life
- Rate constants
- Time



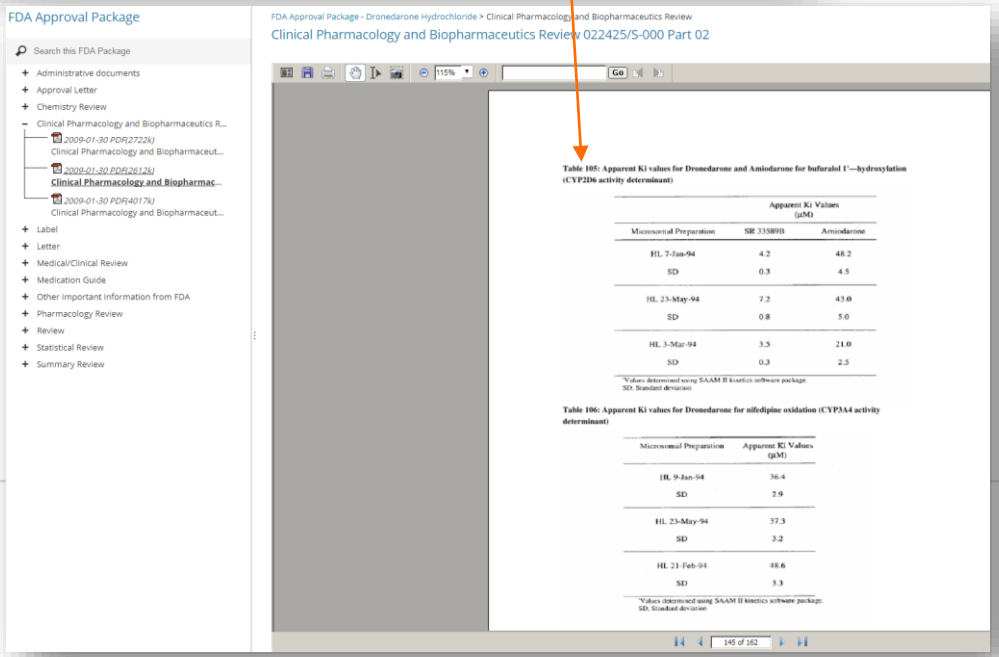
Species

Includes:
- Human
- Vertebrates
  - Birds
  - Fish
  - Mammals

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

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

检索数据，来源于监管机构的官方档案



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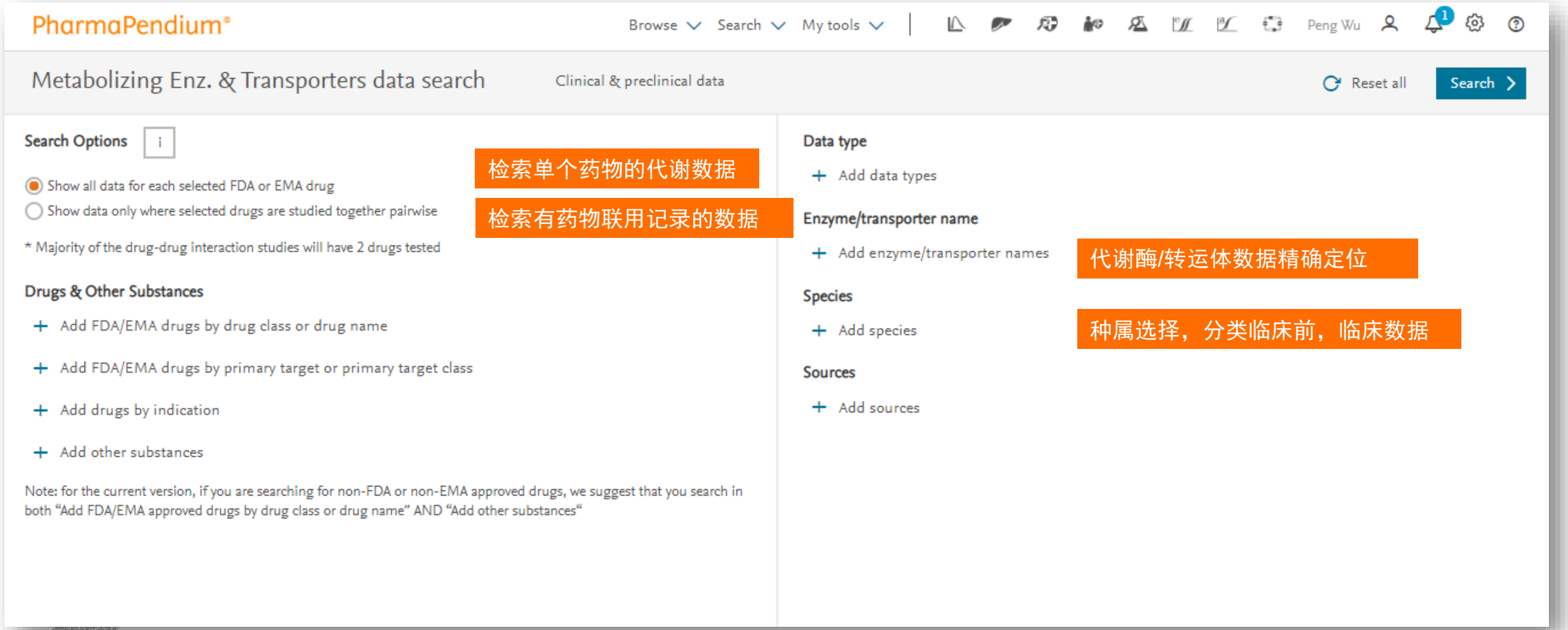
Case 5：运用代谢酶和转运体模块进行数据检索



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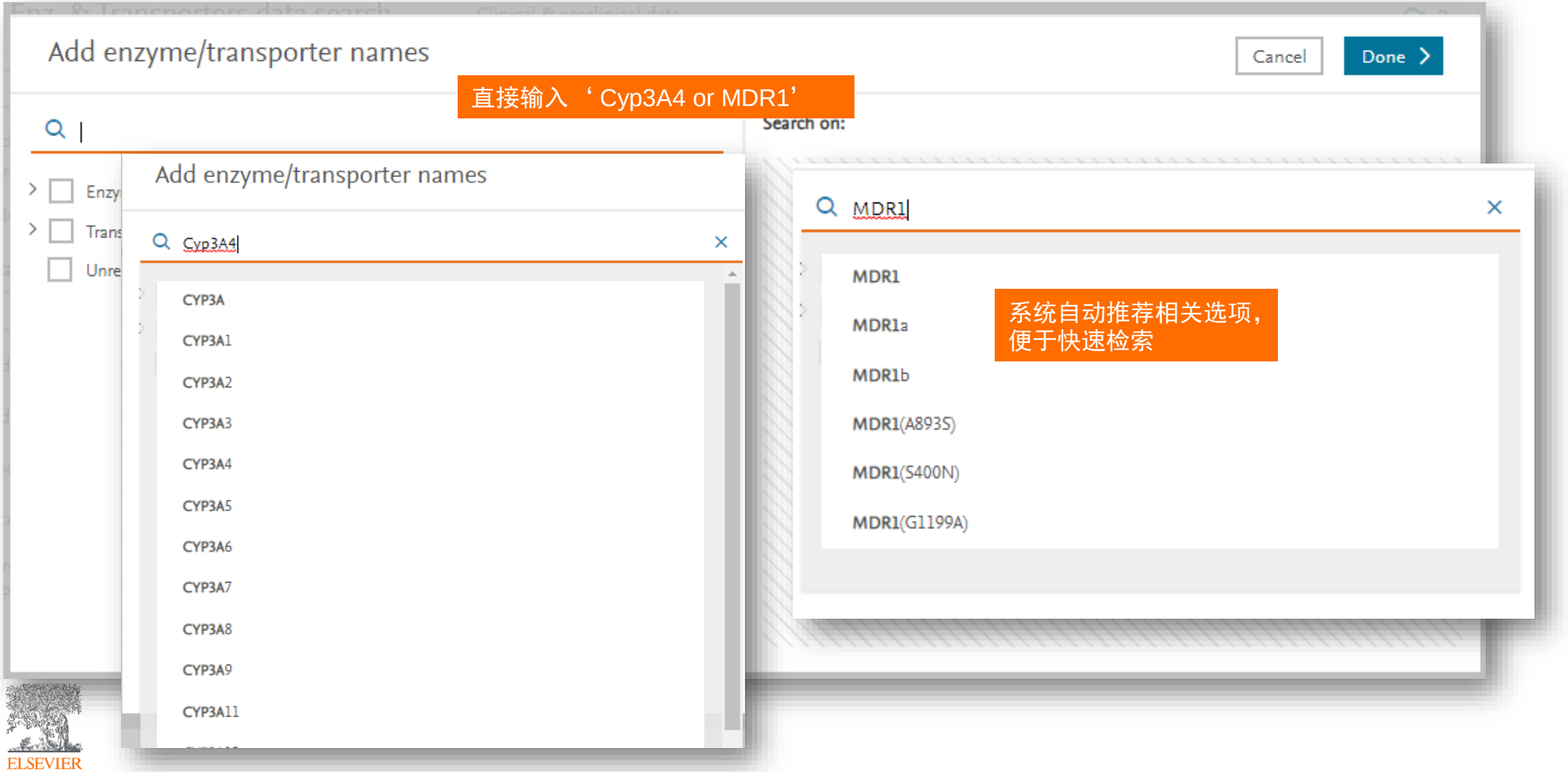
代谢酶和转运体—分类，整理



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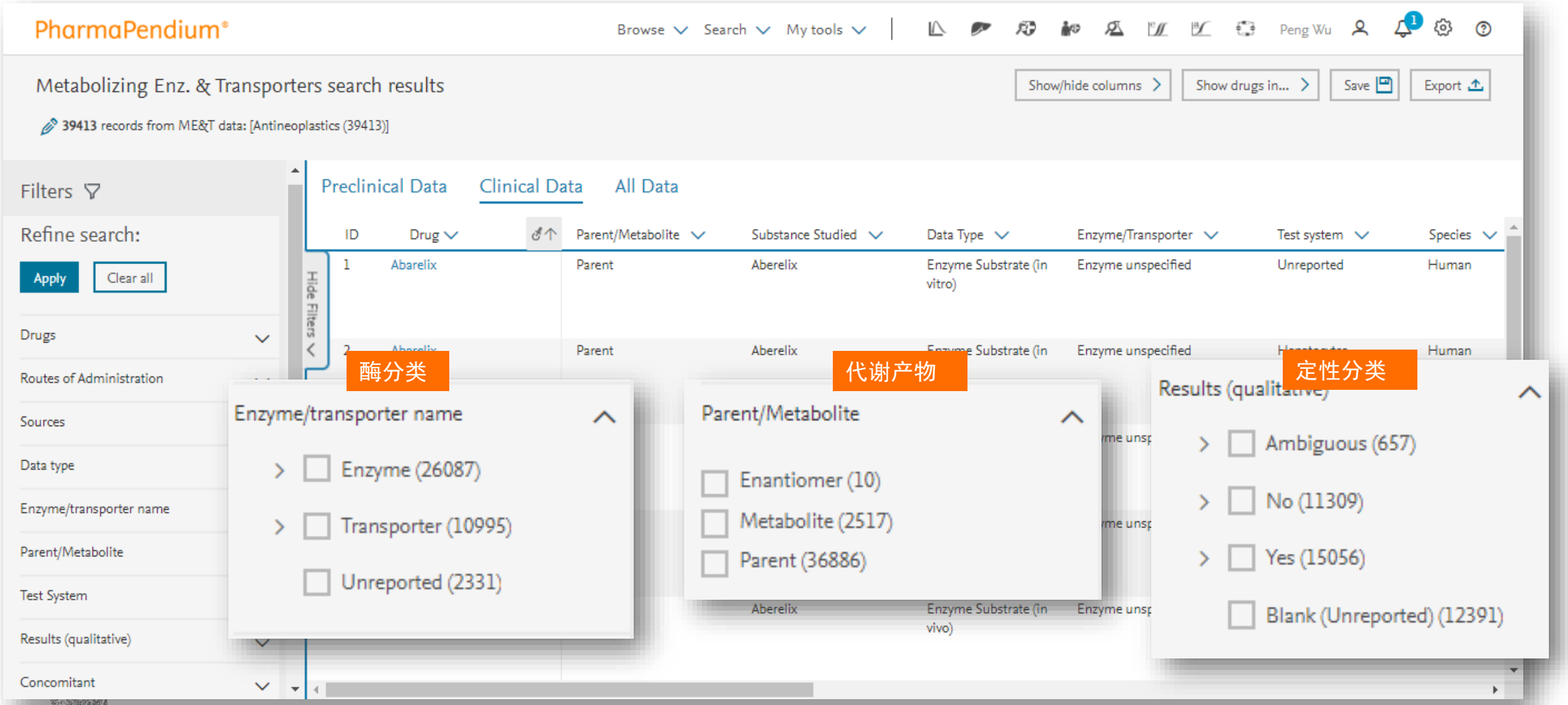
抗肿瘤药物的代谢数据总览



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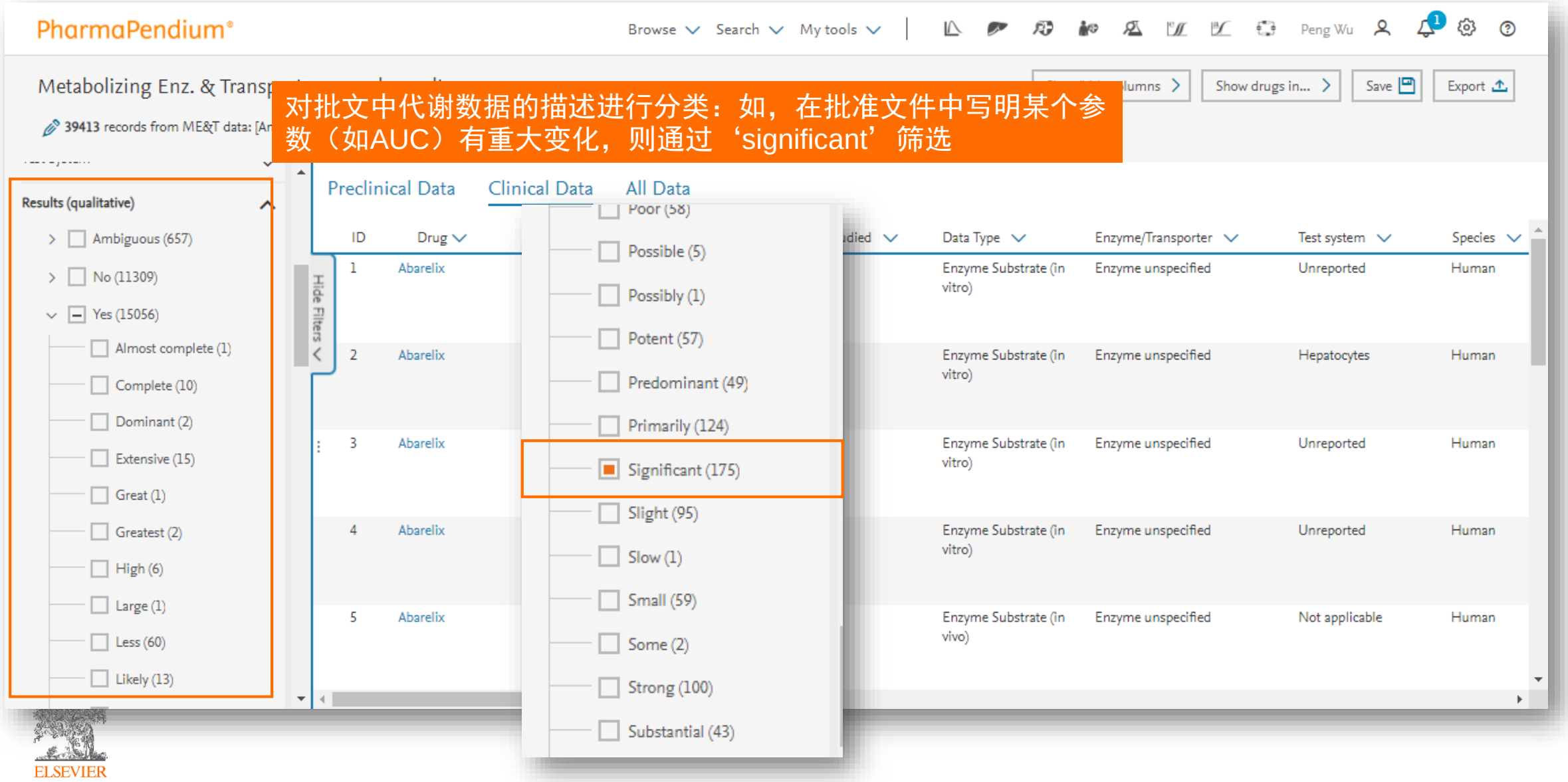
抗肿瘤药物的代谢数据的深度提炼



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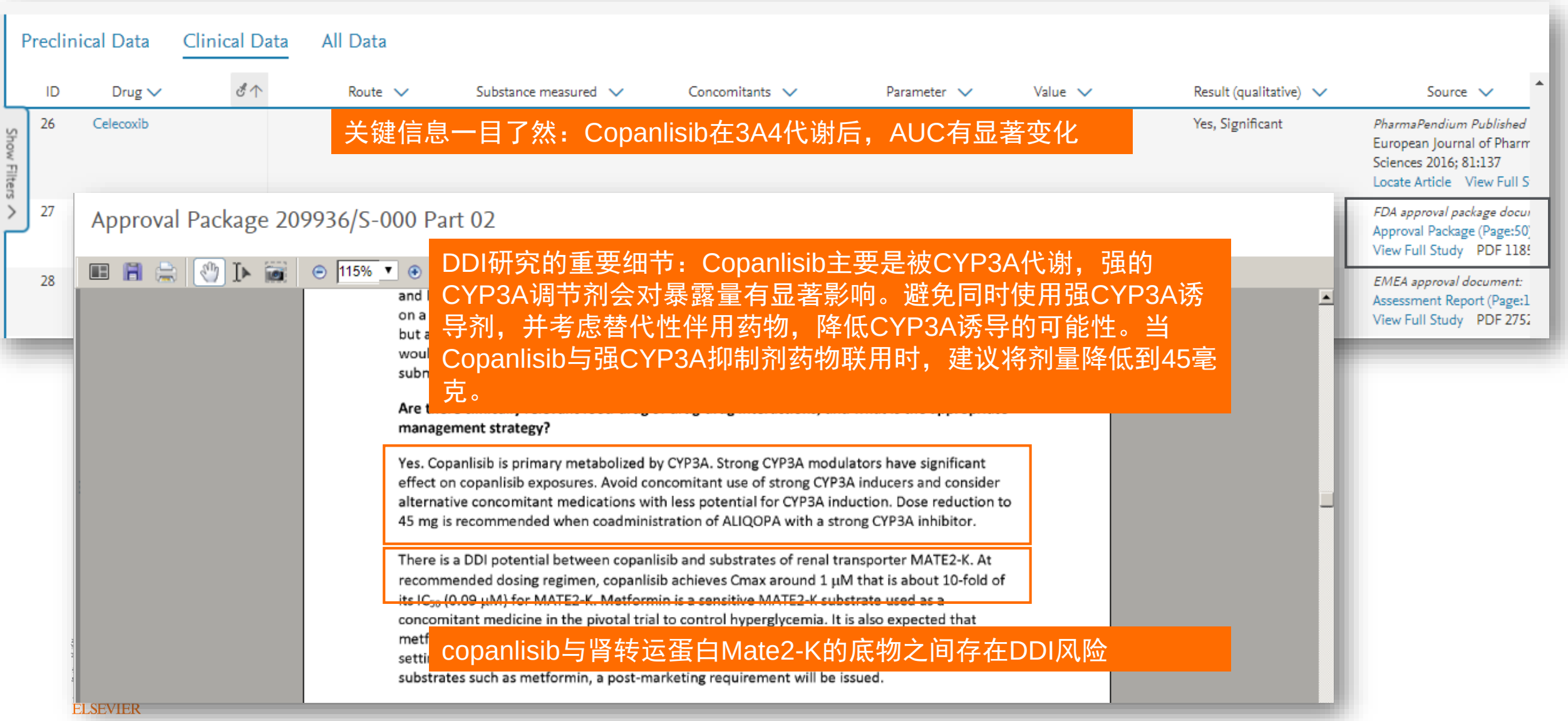
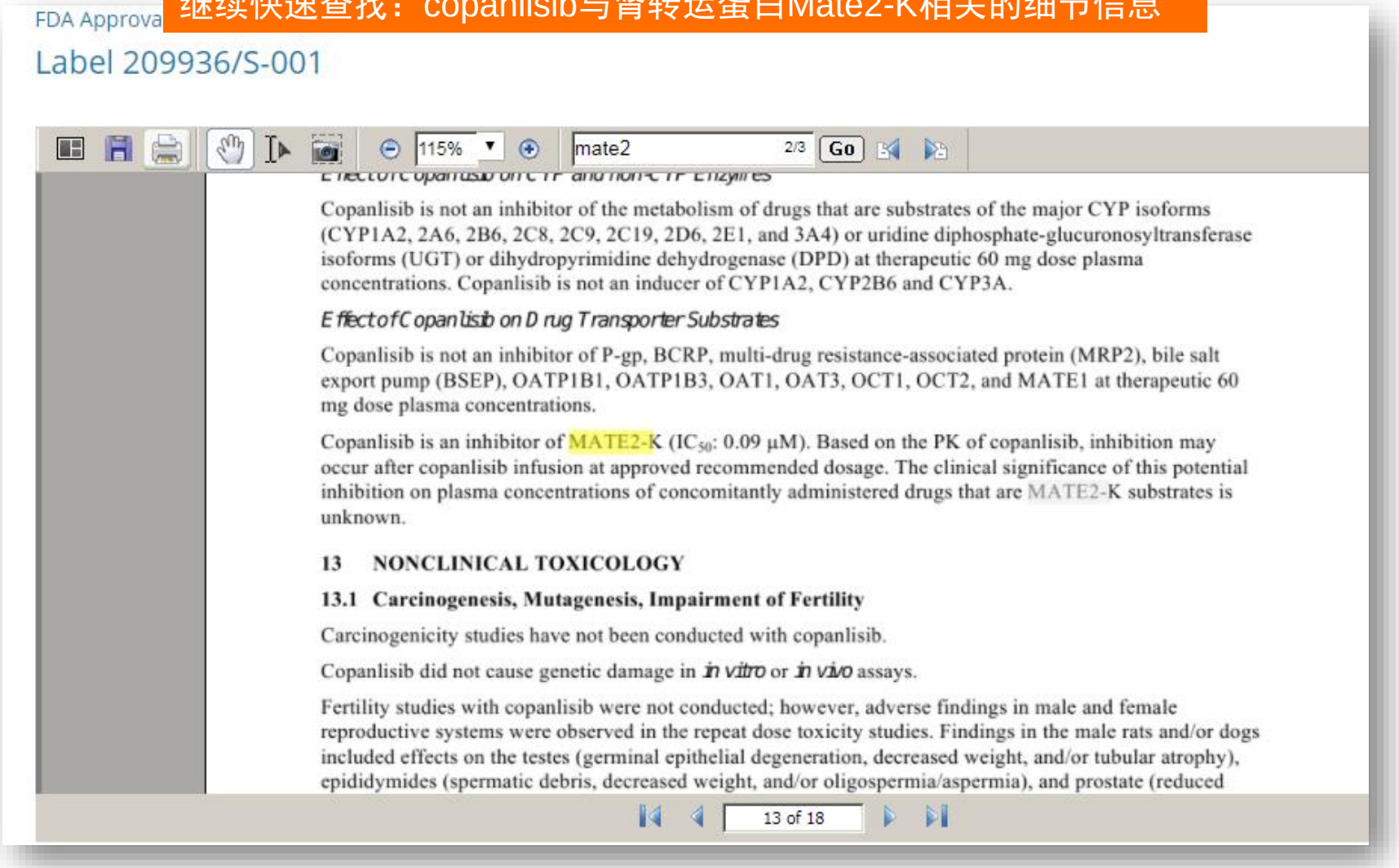
抗肿瘤药物的代谢数据的—细节快速追踪

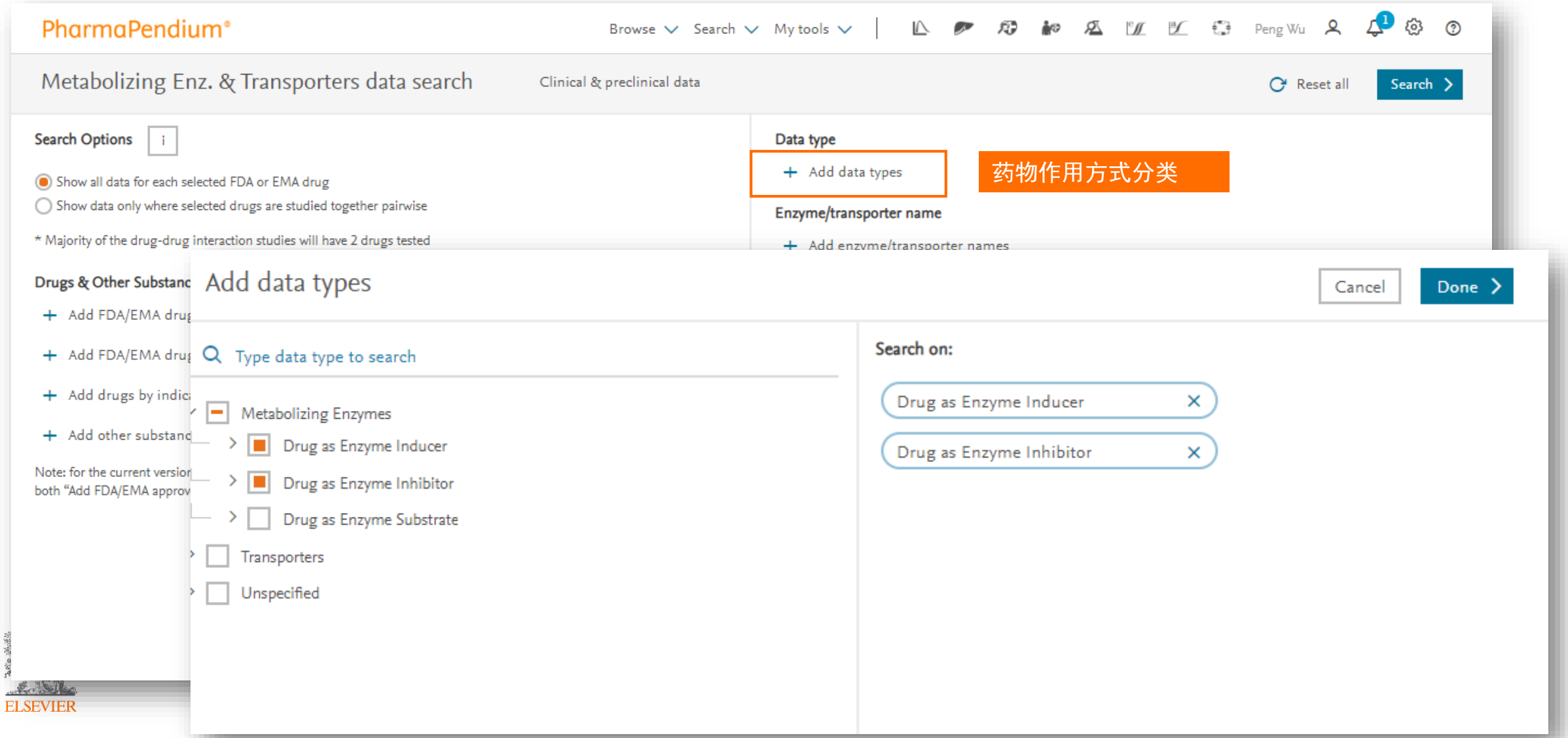


抗肿瘤药物的代谢数据的—更多细节快速追踪

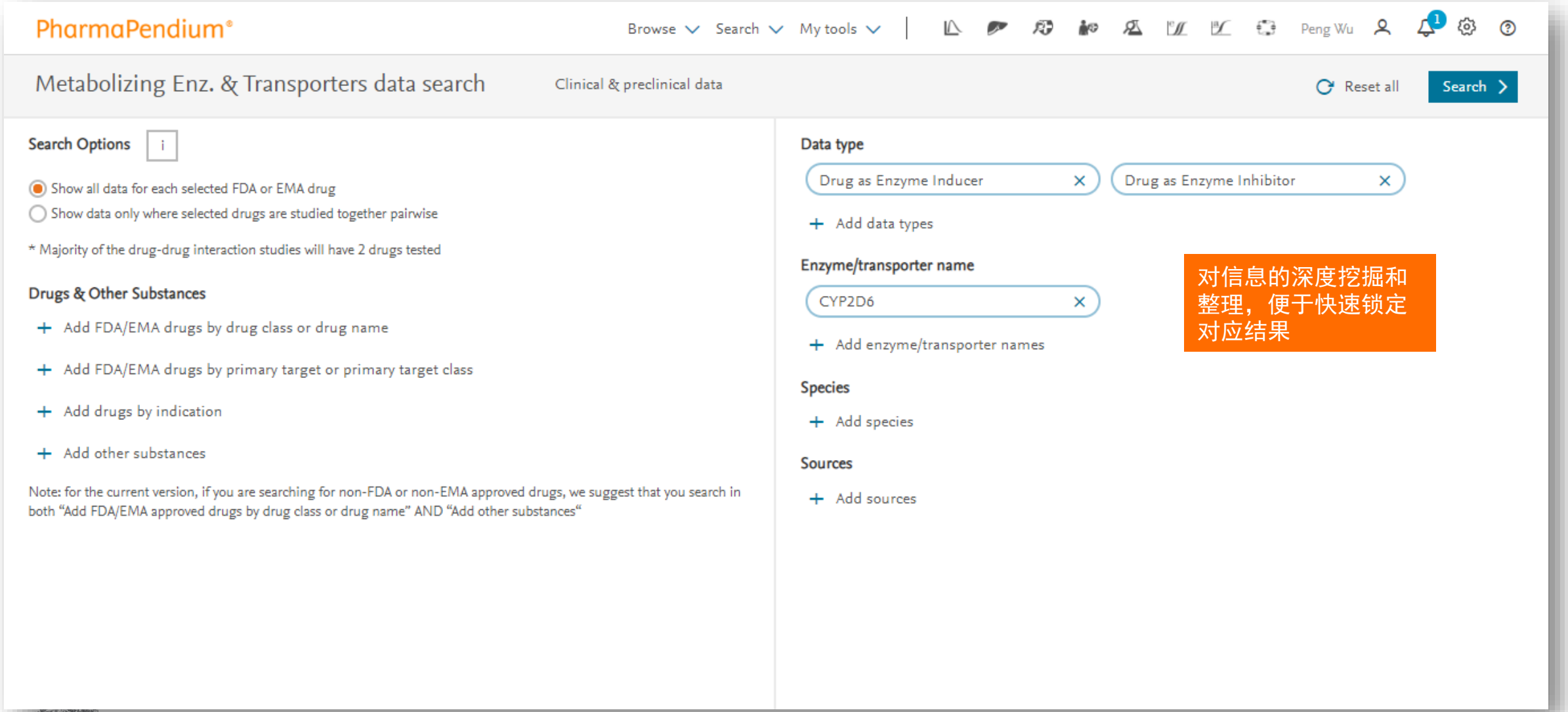
继续快速查找：copanlisib与肾转运蛋白Mate2-K相关的细节信息



Case 6:哪些药物可以与我的药物相互作用，并且由CYP2D6代谢

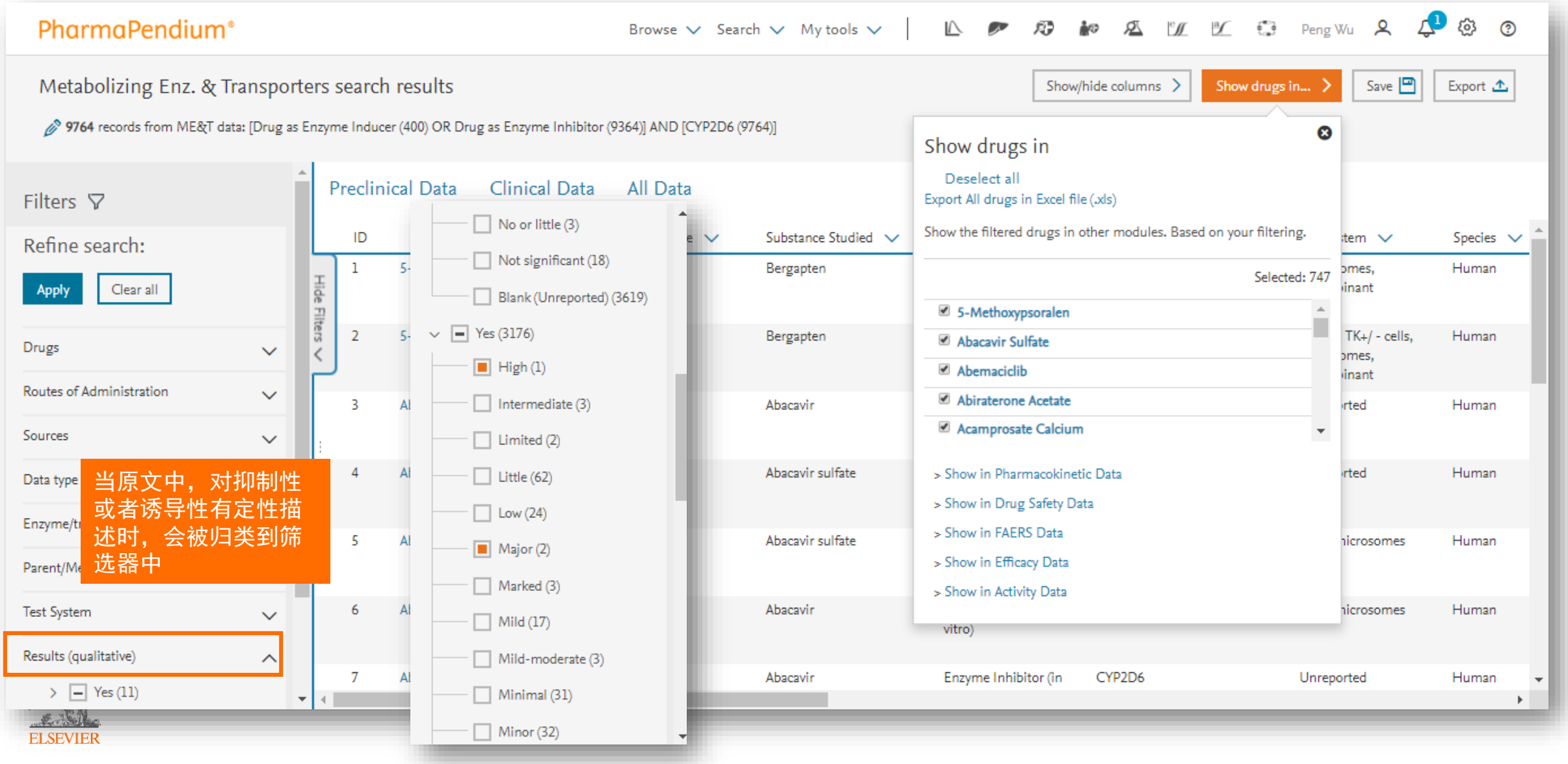


检索CYP2D6有诱导或抑制作用的药物



对信息的深度挖掘和整理，便于快速锁定对应结果

Cyp2D6诱导剂或者抑制剂的检索结果



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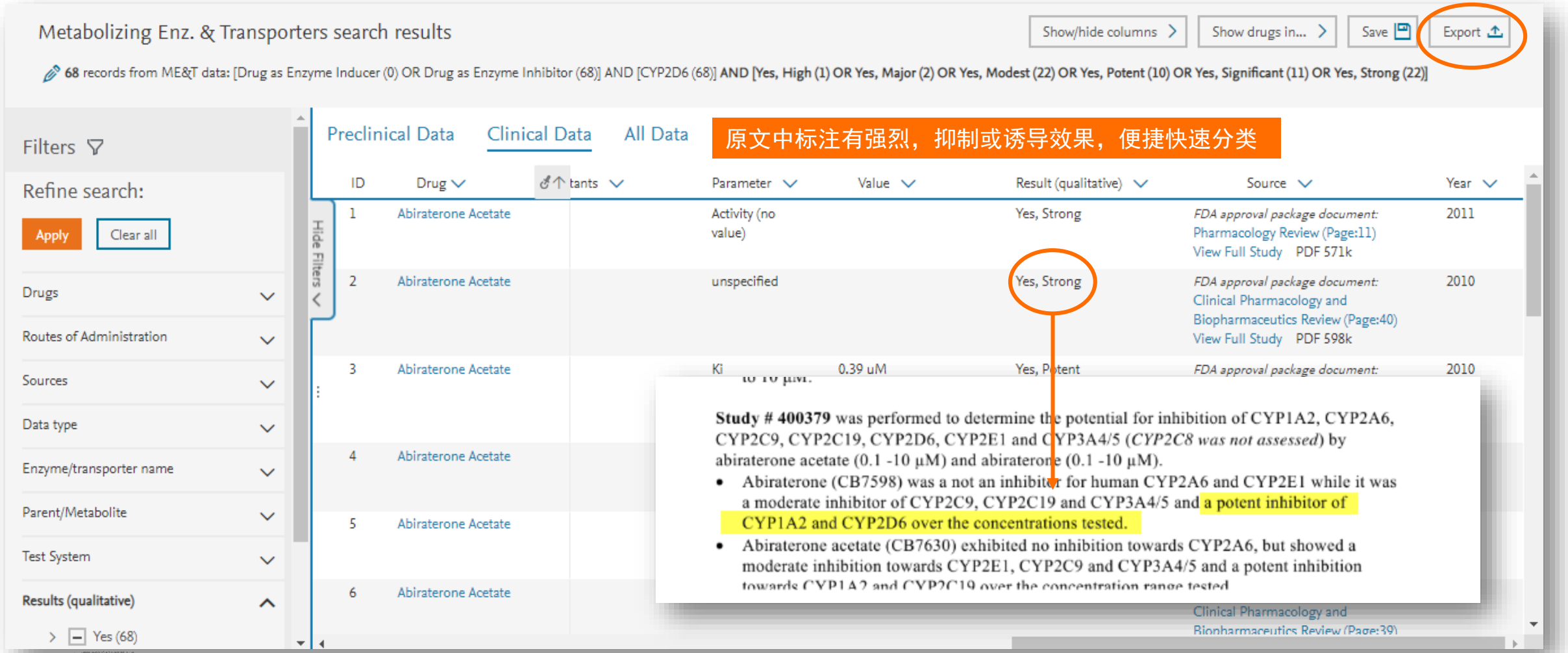
Cyp2D6诱导剂或者抑制剂筛选结果

导出归档对CYP2D6有较严重或诱导的药物数据



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在研药物Cyp2D6为基础的DDI预测

PharmaPendium®

Browse Search My tools | Peng Wu

Proprietary Victim Drug

Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

*Compound name: test 1

Hepatic Metabolism

User Defined
Predicted

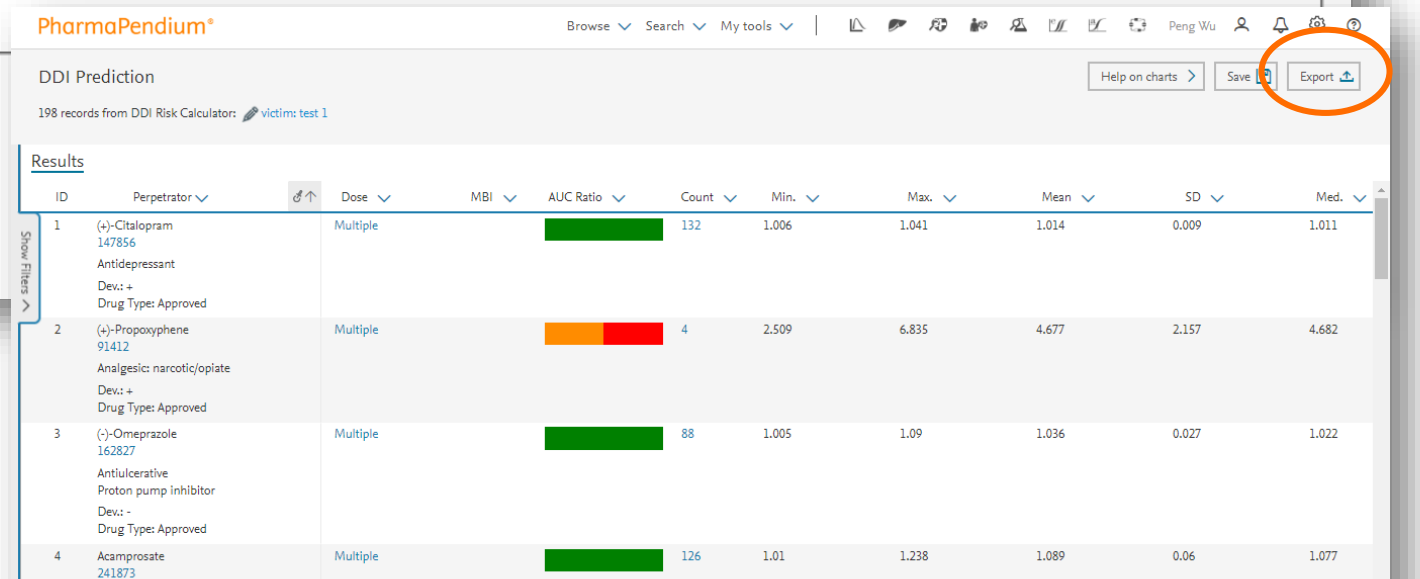
假设在研药物为‘受害药’，主要被CYP2D6代谢

Enzyme(s)	kdeg (min-1)	fmE
CYP2D6	0.000226	0.9
Select		

代谢程度达到90%

Predict interactions

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



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

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哪些Cyp2D6的抑制剂或诱导剂于在研药物存在DDI风险

高风险的侵害药列表

Victim	Perpetrator1			AUC Ratio									
	Name	Therapeutic class	Dose/unit	Min	Max	Mean	SD	Median	5th Per	95th Per	Count	Color	AUC rati
test 1	(+)-Propoxyphene	–Analgesic; narcotic/opiate–	0.6 g	6.834	6.835	6.834	1.507E-4	6.834	6.834	6.835	2		
test 1	Budipine	–Antiparkinsonian–	0.01 g	5.11	5.11	5.11	0.0	5.11	5.11	5.11	1		
test 1	Cimetidine	–Antihistaminic–Antiulcerative–	0.3 g	5.385	6.672	6.052	0.371	6.043	5.501	6.622	180		
test 1	Cimetidine	–Antihistaminic–Antiulcerative–	0.8 g	7.844	8.601	8.276	0.2	8.298	7.884	8.566	1		
test 1	Fluvoxamine	–Antidepressant–	0.05 g	5.423	6.34	5.863	0.282	5.797	5.479	6.327			
test 1	Fluvoxamine	–Antidepressant–	0.1 g	6.058	8.46	7.362	0.723	7.432	6.271	8.411	36		
test 1	Mibefradil	–Antianginal–Antihypertensive–Calcium channel blocker–	0.043 g	0.974	0.992	0.983	0.006	0.981	0.974	0.991	17		
test 1	Mibefradil	–Antianginal–Antihypertensive–Calcium channel blocker–	0.1 g	0.992	0.998	0.995	0.002	0.994	0.992	0.997	17		
test 1	Mibefradil	–Antianginal–Antihypertensive–Calcium channel blocker–	0.15 g	0.995	0.999	0.997	0.001	0.997	0.995	0.998	17		
test 1	Mibefradil	–Antianginal–Antihypertensive–Calcium channel blocker–	0.25 g	0.998	0.999	0.999	5.161E-4	0.998	0.998	0.999	17		
test 1	Nilotinib	–Antineoplastic–	0.8 g	5.625	5.762	5.694	0.068	5.694	5.632	5.755	2		
test 1	Nilotinib	–Antineoplastic–	1.2 g	6.454	6.537	6.496	0.042	6.496	6.458	6.533	2		
test 1	Paroxetine	–Antidepressant–	0.02 g	7.983	9.845	9.266	0.369	9.343	8.57	9.705	126		
test 1	Paroxetine	–Antidepressant–	0.03 g	9.197	9.913	9.634	0.174	9.674	9.373	9.889	42		
test 1	Paroxetine	–A											
test 1	Pazopanib	–A											
test 1	Propafenone	–A											
test 1	Quinidine	–A											
test 1	Quinidine	–A											
test 1	Quinidine	–A											
test 1	Rilpivirine	–A											
test 1	Rilpivirine	–A											
test 1	Rilpivirine	–A											
test 1	Rilpivirine	–A											
test 1	Taranabant	–A											
test 1	Terbinafine	–A											
test 1	Ticlopidine	–A											

Overview | Input P

CYP2D6抑制剂或者诱导剂

Export date: 19-08-2019

Metabolizing Enzymes And Transporters Data Search Results For: Data type: [Drug as Enzyme Inducer (0) OR Drug as Enzyme Inhibitor (68)] AND Enzyme/Transporter name: [CYP2D6 (68)] AND

Total results: 68

Sort order: Drug (Ascending);

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

Metabolizing Enzymes And Transp

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Met代谢数据检索及DDI预测的应用

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

在药物的研发过程中会持续的评估DDI的情况

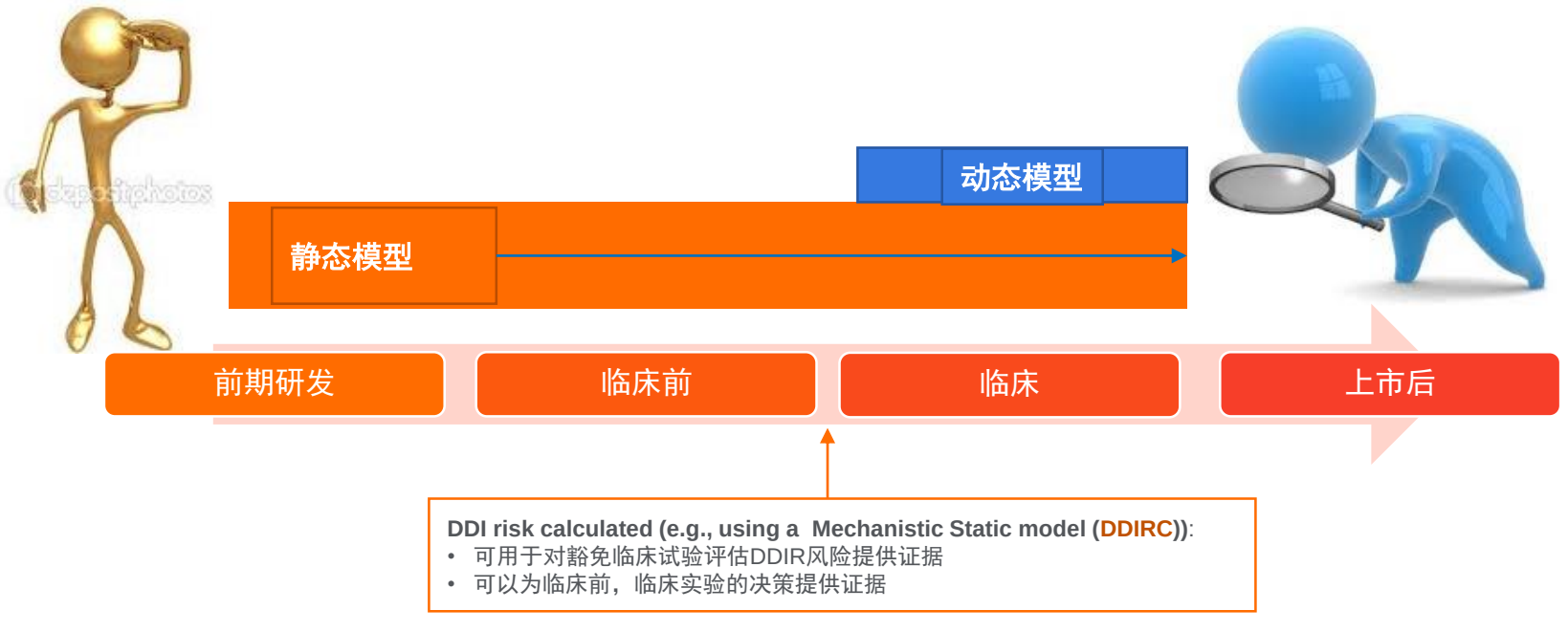
FDA建议在DDI评估时，应当逐步的，以模型为基础制定评估方案

早起开发阶段中: 更完善的评估策略

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

后期研发阶段: 更细致的评估

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



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

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

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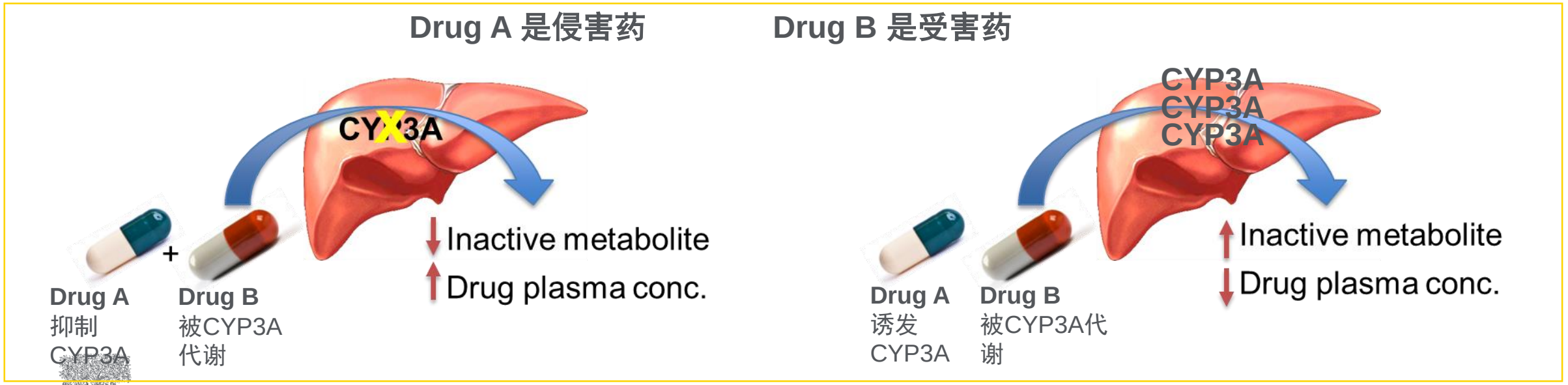
PharmaPendium DDI 风险预测计算器(DDIRC)

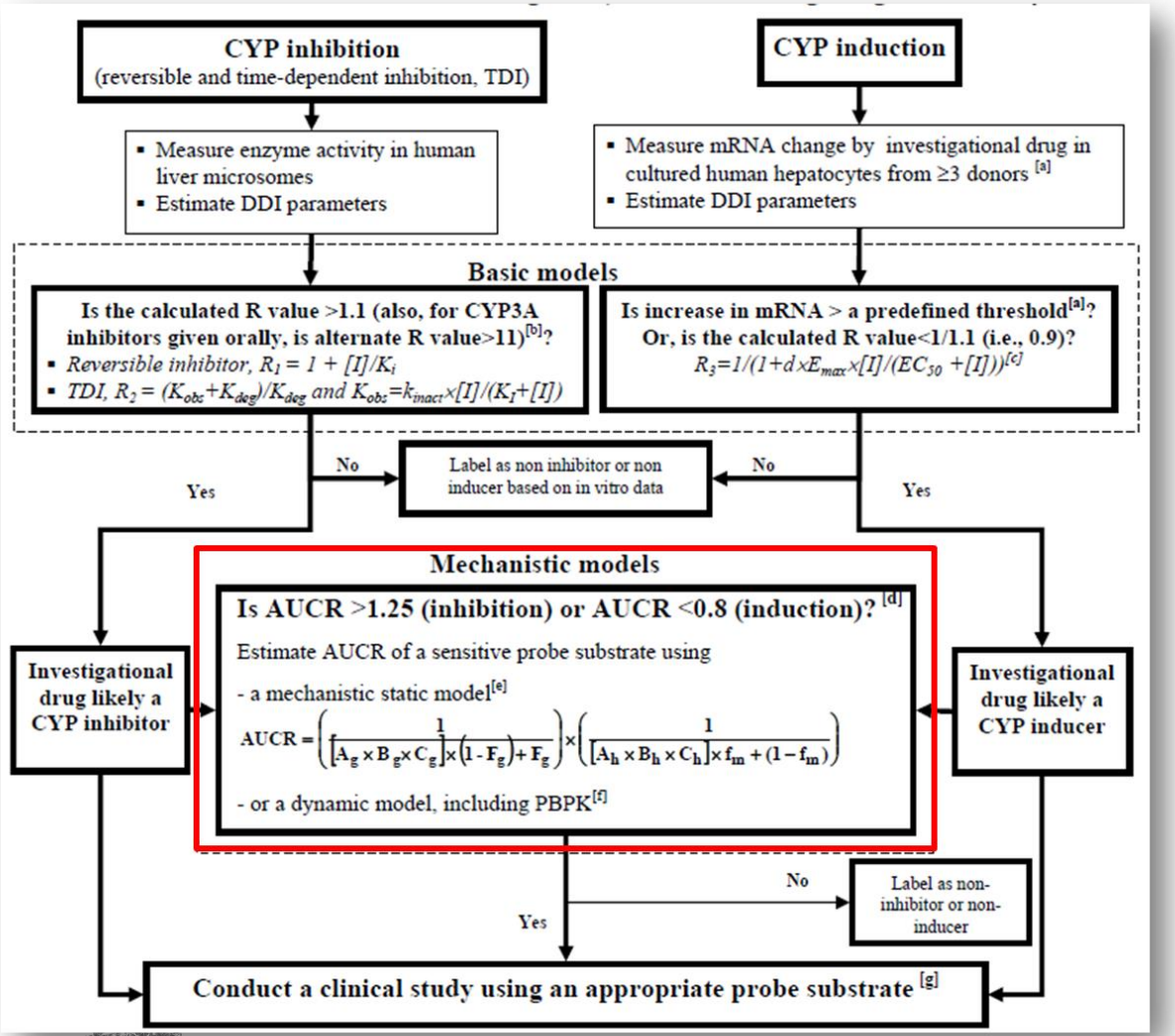
预测潜在的DDI风险（受害药或者侵害药）

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

侵害药：会影响其他药物的药代动力学
受害药：由于与其他药物的相互作用，而影响了自身的药代动力学



DDIRC 是依据FDA的指南设计的



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

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

DDIRC 辅助 DDI 研究及临床实验决策

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

Real example of how DDIRC impacted clinical trial design

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

Significant DDI predicted with some sensitive substrates of CYP3A4

CYP3A4 substrates **prohibited** from clinical trials

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

Understanding how to manage DDI risks impacts CT design and may allow marketing of a drug that would otherwise have an unacceptable level of risk

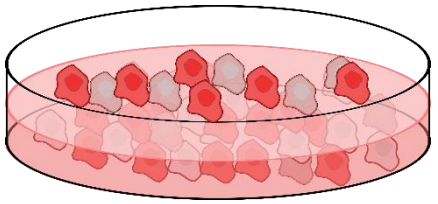
How does the DDI Risk Calculator work?

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

Some background:

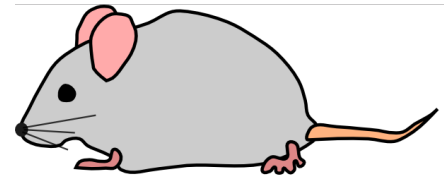
In vitro refers to techniques used to perform a given procedure outside a living organism – e.g., experiments performed in a test tube or cell culture

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



In vitro

In vivo



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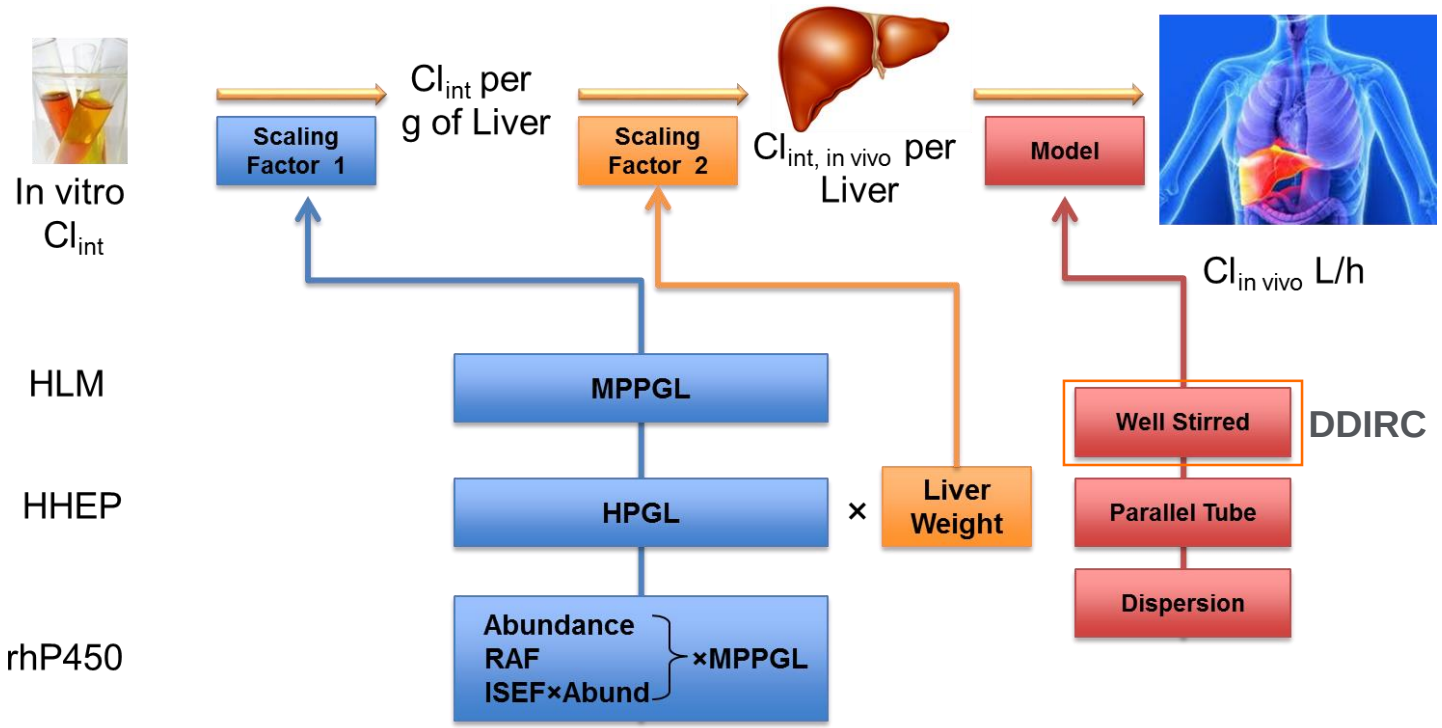
DDI计算器如何计算

运用不同的体外数据来推测体内的可能出现的结果



Predicting hepatic clearance

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

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

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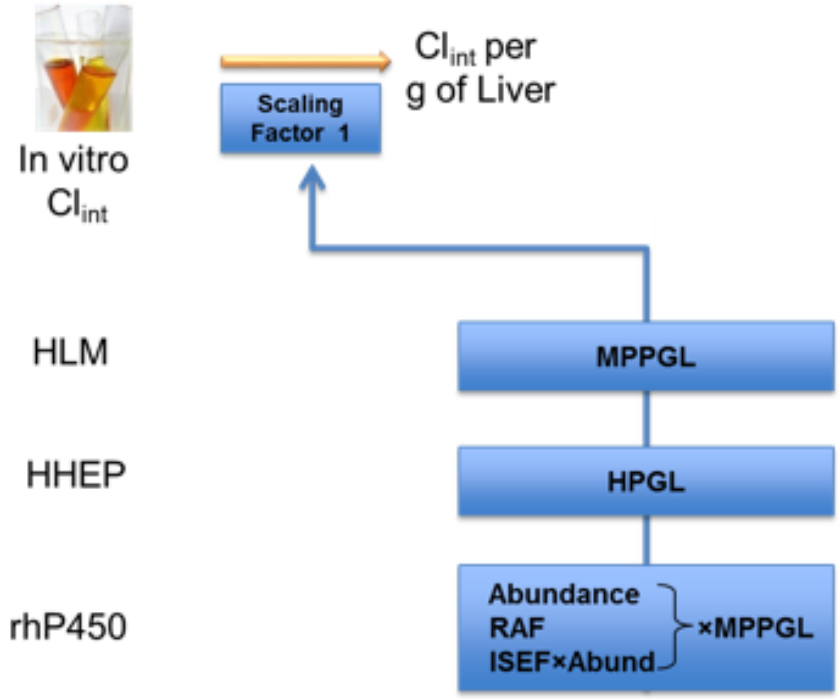
数据模型的应用

Scaling Factor 1



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

药物代谢的体外动力学研究（测量km和vmax）的数据用于评估肝药物清除率

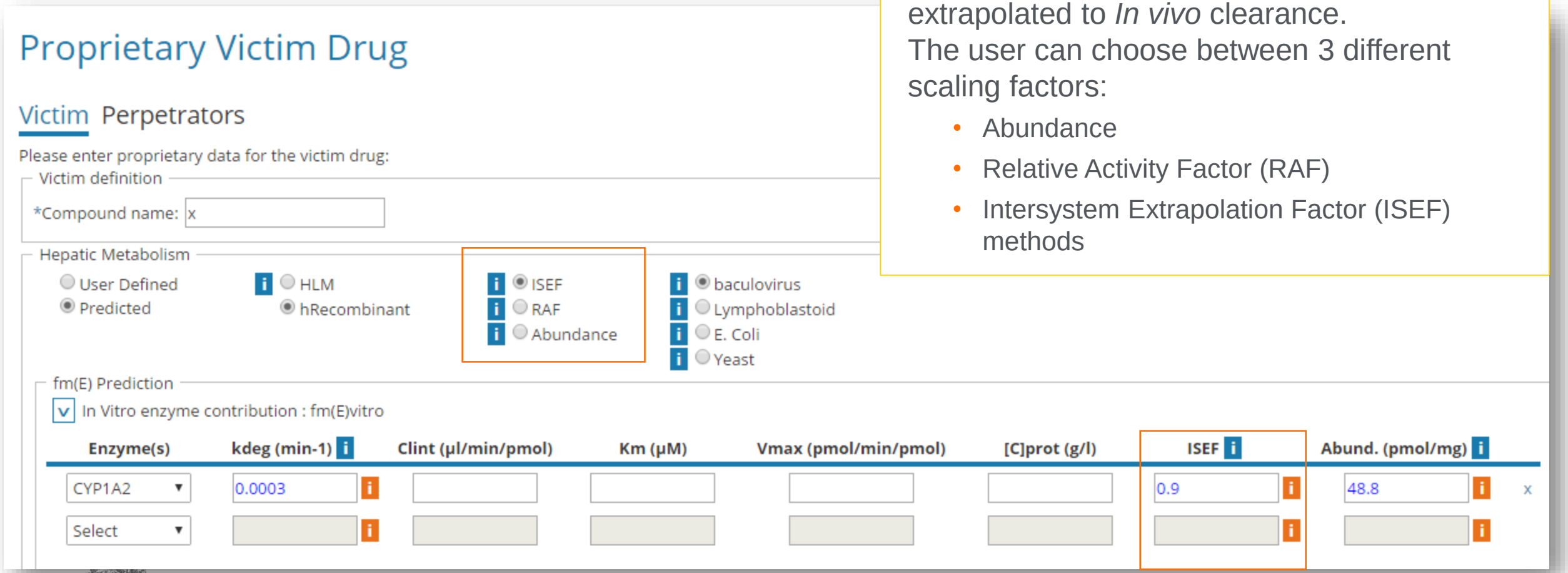
There are different *In vitro* approaches using different human derived materials:

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

数据模型的应用
Scaling Factor 1 (continued)

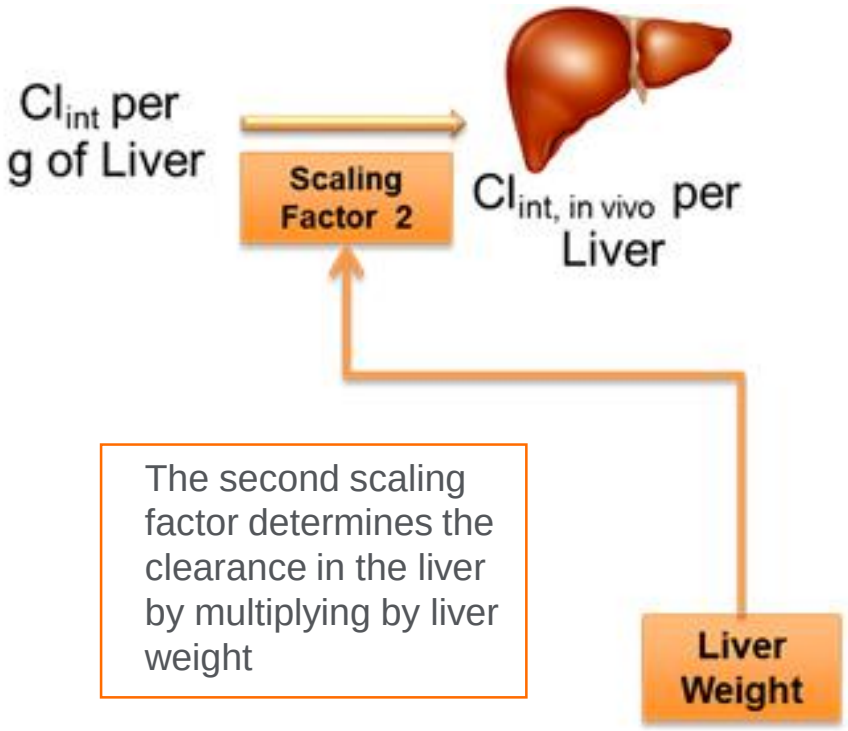
Results from recombinant enzyme experiments are scaled up to human liver microsomes (HLM) **using values from the DDI Risk Calculator** before they are extrapolated to *In vivo* clearance.
The user can choose between 3 different scaling factors:

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



数据模型的应用

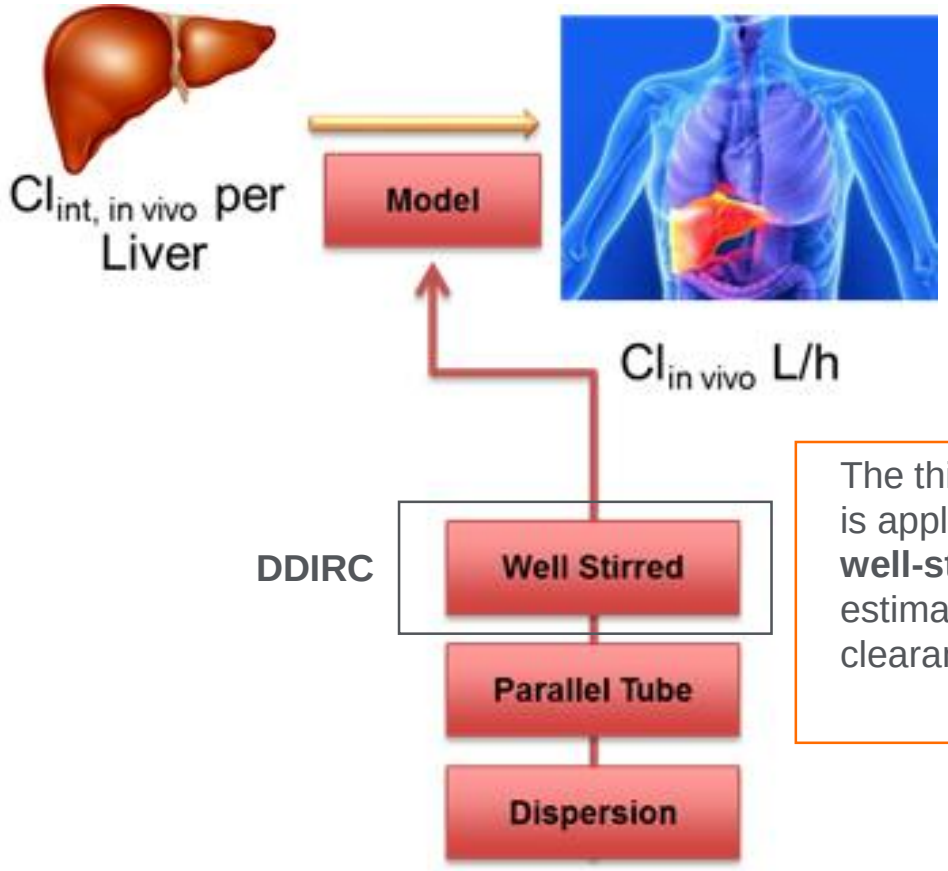
Scaling Factor 2



The second scaling factor determines the clearance in the liver by multiplying by liver weight

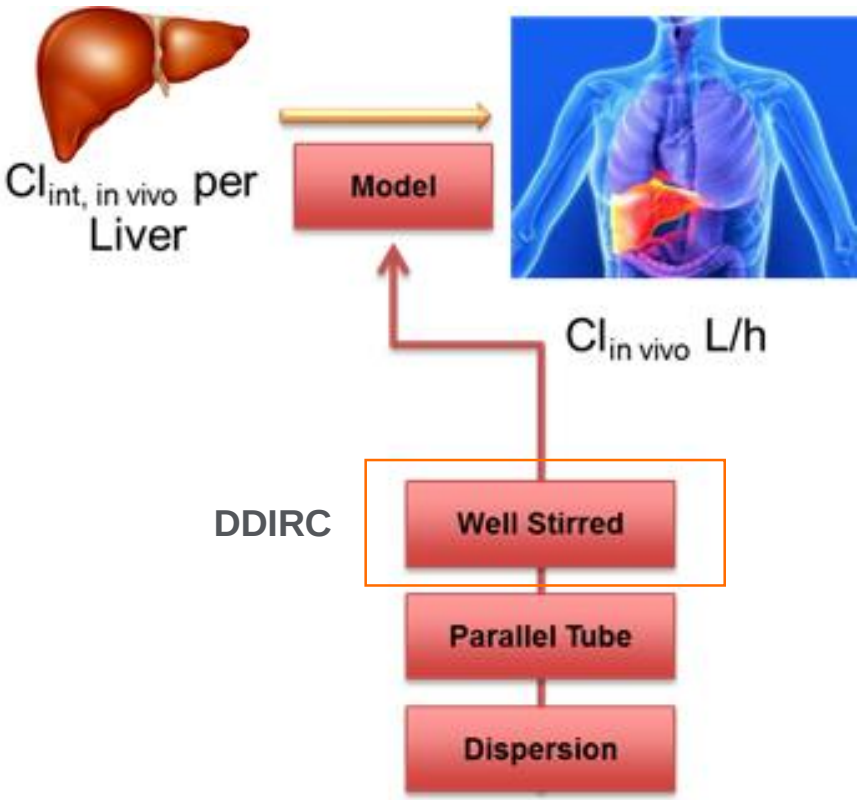
数据模型的应用

Scaling Factor 3



The third scaling factor is application of the **well-stirred model** to estimate hepatic drug clearance

DDIRC 对于肝清除率计算使用 Well-Stirred模型



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

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

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

充分混合模型是估计肝脏清除率最常用的模型。.

- 但是会导致比较轻微的过度评估DDIs风险

Handbook of Essential Pharmacokinetics, Pharmacodynamics and Drug Metabolism for Industrial Scientists 2002, Kwon, Younggil

DDIRC Demo: Test compound as a victim

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Empowering Knowledge

测试化合物为受害药物

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

M2
MW: 475.6

Test compound
MW: 473.6

重组固有清除率（Recombinant Intrinsic Clearance）
细胞系统（Cell system: Insect cells Infected with Bacculovirus）

- **M1**: 3A4 Km=8.6μM Vmax=0.87 pmol/min/pmol [C] prot=0.5 mg/ml

- **M2**: 3A4 Km=32μM Vmax=3 pmol/min/pmol [C] prot=0.5 mg/ml
  2C9 Km=4 μM Vmax=0.1 pmol/min/pmol [C] prot=0.5 mg/ml

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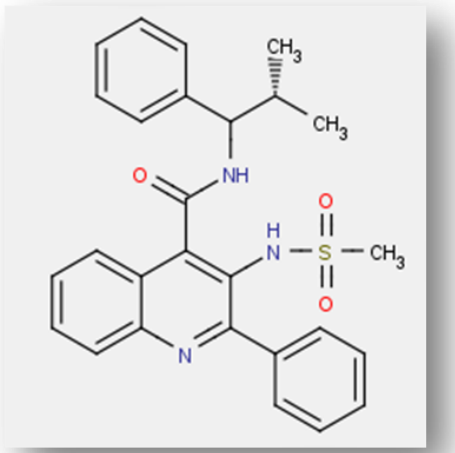
测试化合物的物化性质以及血浆结合率



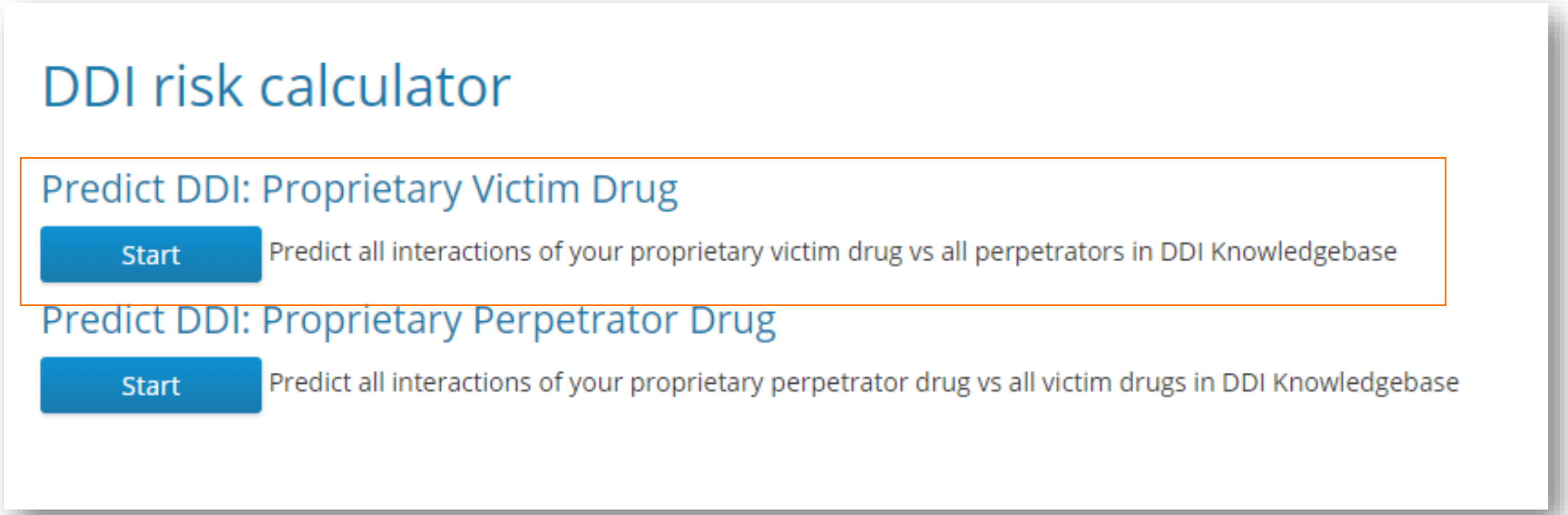
- **Binding**:
  - fu (plasma): 0.4-0.5
  - Rb: 0.55 Default

- **Physchem**

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

Values powered by JChem from ChemAxon

Predict DDIs with the proprietary drug as a victim



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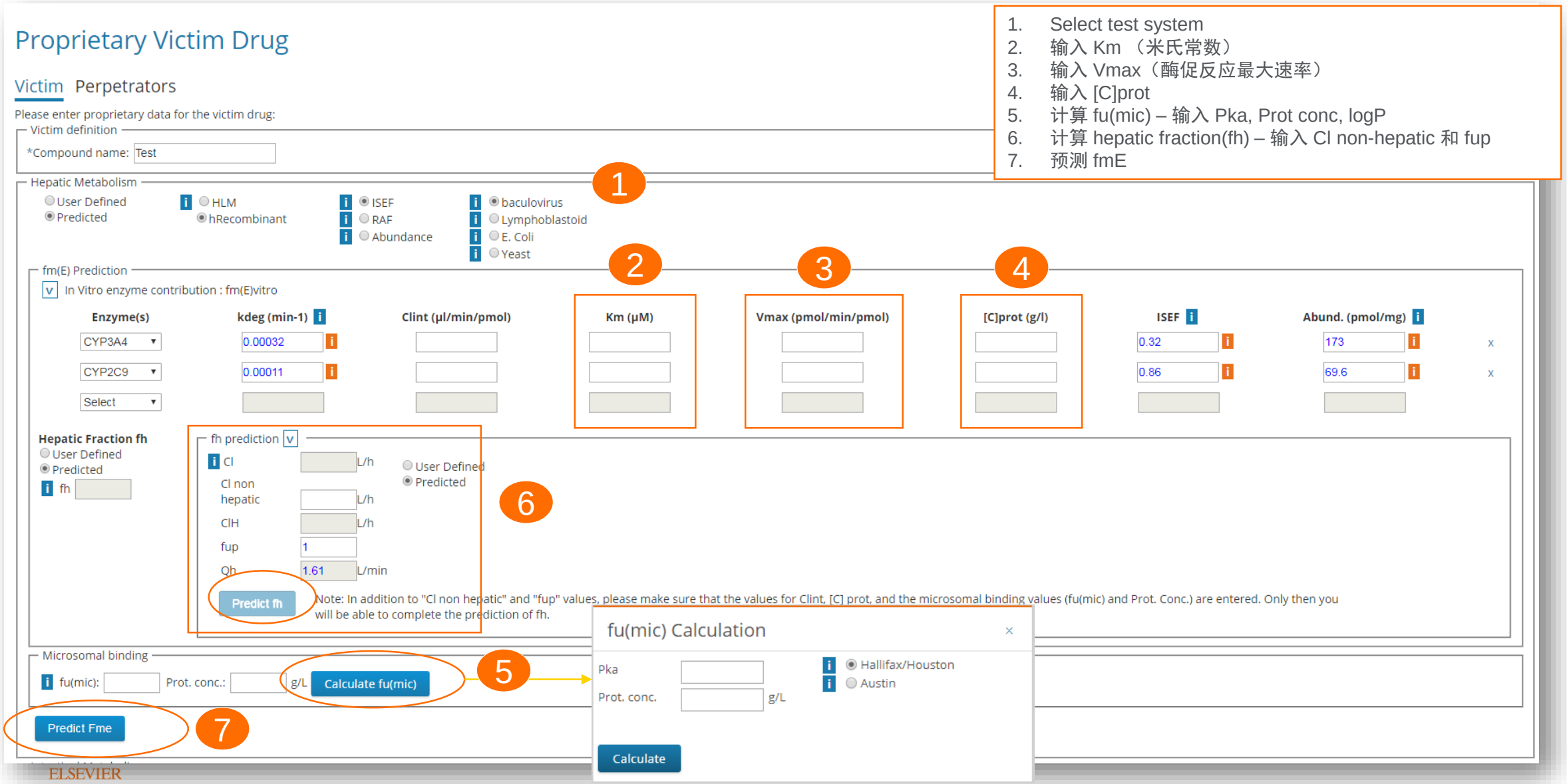
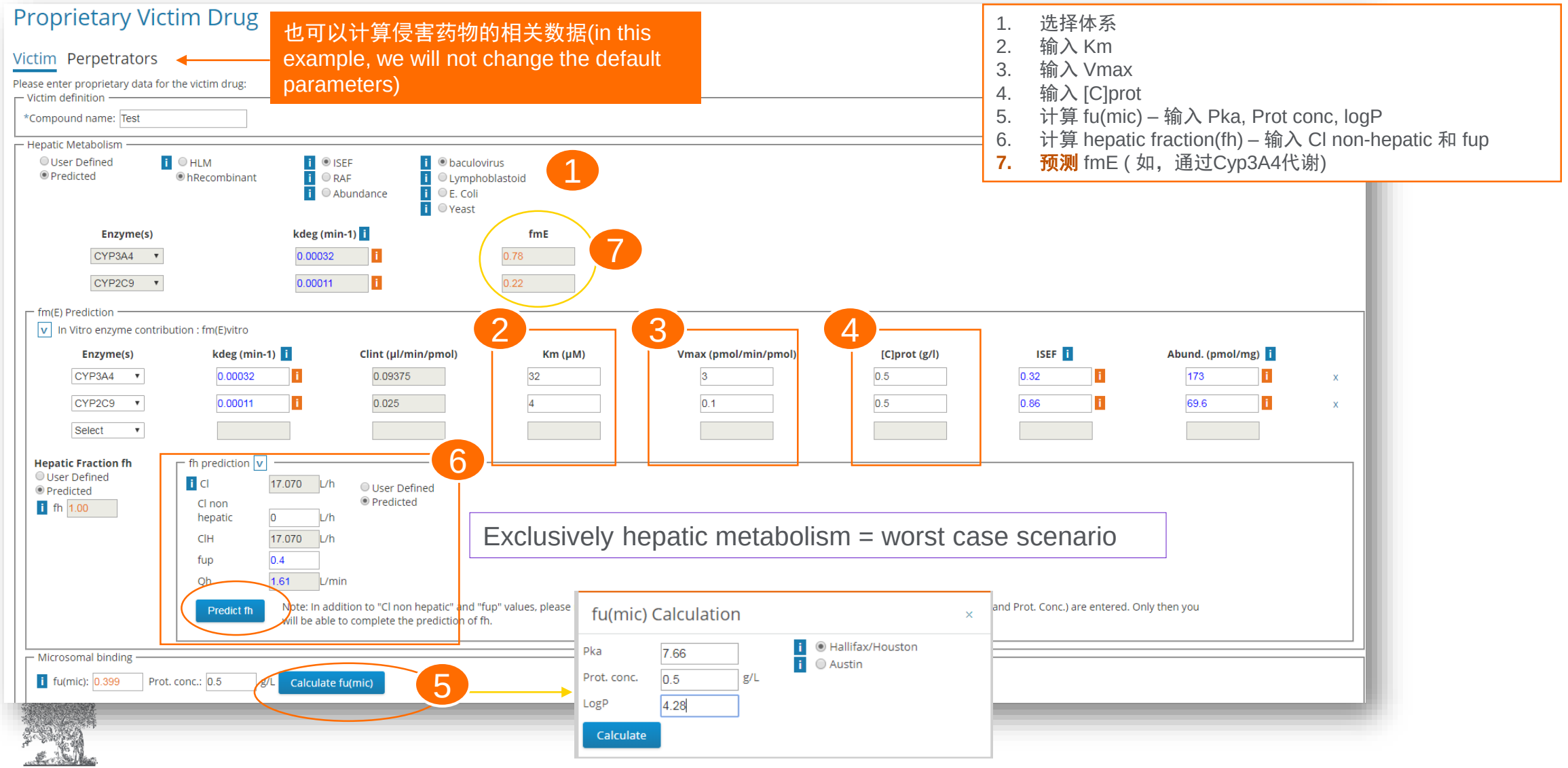
通过输入数据来预测FmE



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

侵害药物FmE预测



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

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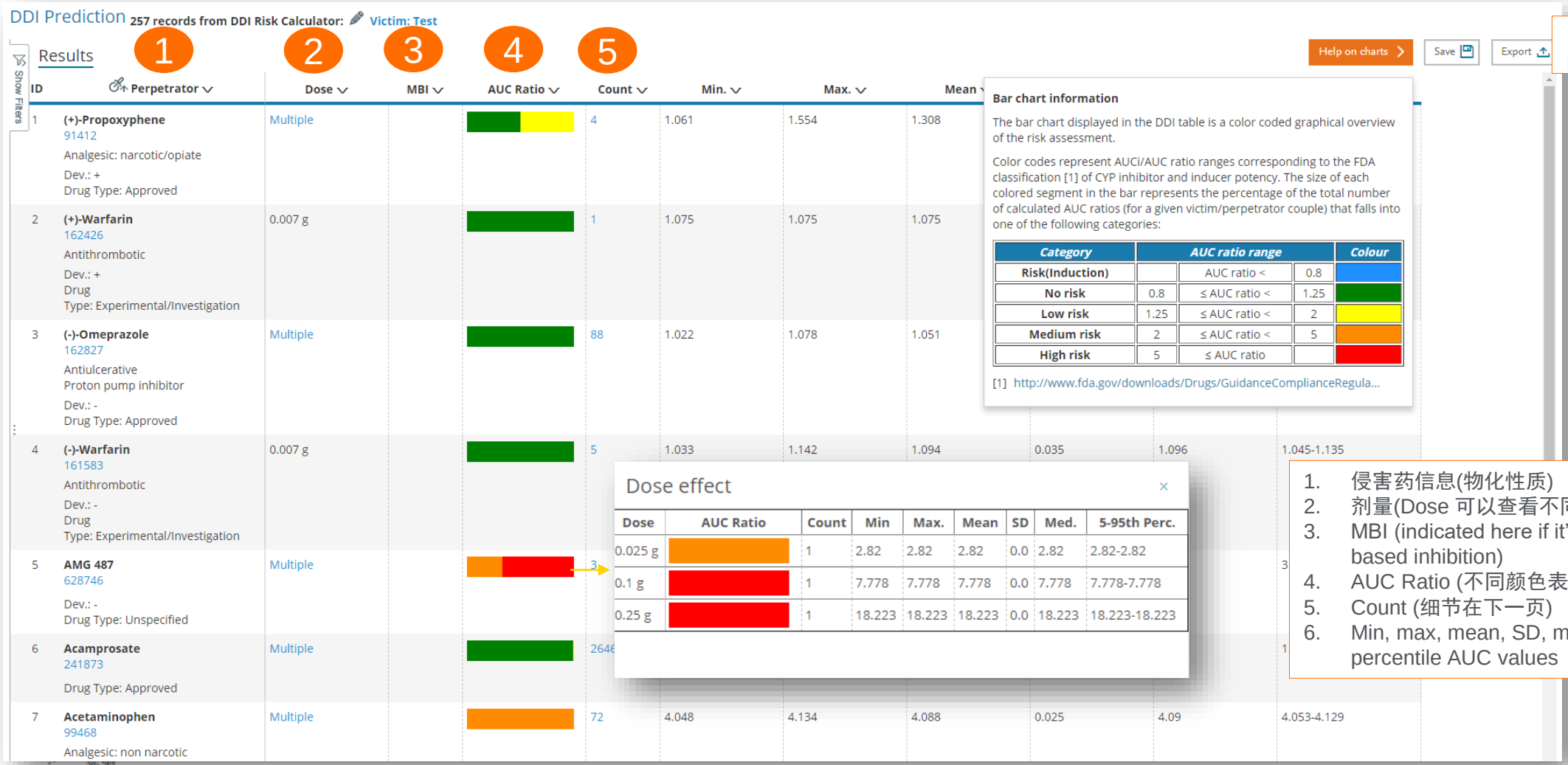
Modify intestinal metabolism data (if required)

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

Predict interactions

257 侵害药结构 – 点击蓝色链接都有细节



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

‘count’ 选项的细节

蓝色连接会有更多细节

DDI Results details

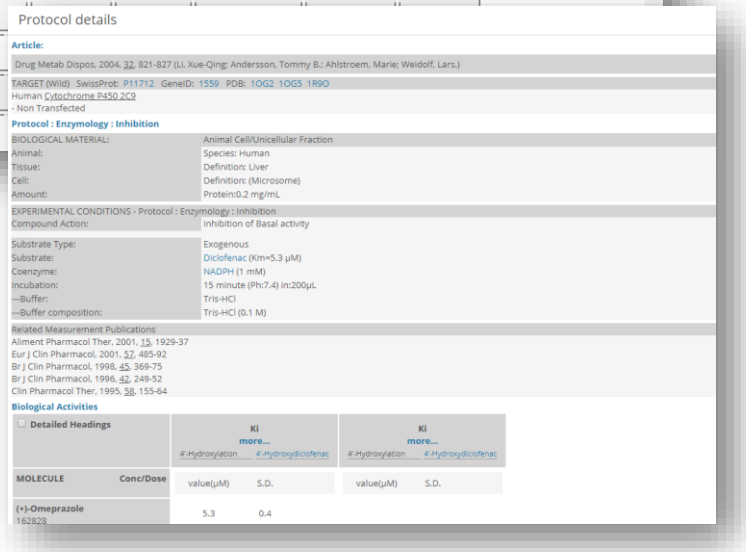
Export

Victim: Test | Perpetrator: (-)-Omeprazole

AUCi/AUC	F'g/Fg	Enzyme	fm(E)	Fg	[Iu]g (μM)	I Optimized [I] (μM)	Ki (μM)				Dose	Cmax (μM)	kabs (min-1)	Fa.Fg	Qh	Fu(blood)	Rb	Kb
							Value	[C]prot	Substrate	fu(mic)								
1.03	1	CYP2C9	0.22		2.622	+ 1.77	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.014	1	1.61	1	0.55	1
1.03	1	CYP3A4	0.78		1.226	+ 1.51	46.6	0.2 g/L	Midazolam		0.02 g	+ 2.33	+ 0.006	1	1.61	1	0.55	1
1.067	1	CYP2C9	0.22		2.452	+ 3.009	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.64	+ 0.006	1	1.61	1	0.55	1
1.067	1	CYP3A4	0.78		5.244	+ 3.529	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.64	+ 0.014	1	1.61	1	0.55	1
1.068	1	CYP2C9	0.22		2.452	+ 3.047	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.71	+ 0.006	1	1.61	1	0.55	1
1.068	1	CYP3A4	0.78		5.244	+ 3.568	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.71	+ 0.014	1	1.61	1	0.55	1
1.026	1	CYP2C9	0.22		1.226	+ 1.13	81.5	0.2 g/L	Diclofenac		0.02 g	+ 1.64	+ 0.006	1	1.61	1	0.55	1
1.026	1	CYP3A4	0.78		2.622	+ 1.391	46.6	0.2 g/L	Midazolam		0.02 g	+ 1.64	+ 0.014	1	1.61	1	0.55	1
1.04	1	CYP2C9	0.22		2.452	+ 2.046	81.5	0.2 g/L	Diclofenac		0.04 g	+ 2.89	+ 0.006					
1.04	1	CYP3A4	0.78		2.452	+ 2.046	46.6	0.2 g/L	Midazolam		0.04 g	+ 2.89	+ 0.006					
1.034	1	CYP2C9	0.22		1.226	+ 1.51	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.006					

预测是输入的数据值

点击数字了，可以看到该结构是依据什么数据来源进行计算



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导出数据-结果总览

Victim	Perpetrator1			AUC Ratio							
	Name	Therapeutic class	Dose/unit	Min	Max	Mean	SD	Median	5th Perc.	95th Perc.	Count
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.065 g	1.061	1.062	1.061	5.003E-4	1.061	1.061	1.062	2
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.6 g	1.554	1.554	1.554	4.065E-5	1.554	1.554	1.554	2
Test	(+)-Warfarin	~Antithrombotic~	0.007 g	1.075	1.075	1.075	0.0	1.075	1.075	1.075	1
Test	(-)-Omeprazole	~Antiulcerative~Proton pump inhibitor~	0.02 g	1.022	1.038	1.032	0.004	1.033	1.023	1.037	24
Test	(-)-Omeprazole	~Antiulcerative~Proton pump inhibitor~	0.04 g	1.03	1.078	1.059	0.013	1.062	1.034	1.075	64
Test	(-)-Warfarin	~Antithrombotic~	0.007 g	1.033	1.142	1.094	0.035	1.096	1.045	1.135	5
Test	AMG 487		0.025 g	2.82	2.82	2.82	0.0	2.82	2.82	2.82	1
Test	AMG 487		0.1 g	7.778	7.778	7.778	0.0	7.778	7.778	7.778	1
Test	AMG 487		0.25 g	18.223	18.223	18.223	0.0	18.223	18.223	18.223	1
Test	Acamprosate		0.3 g	1.012	1.086	1.046	0.02	1.043	1.017	1.079	441
Test	Acamprosate		0.5 g	1.017	1.141	1.075	0.033	1.069	1.026	1.129	441
Test	Acamprosate		0.666 g	1.019	1.184	1.095	0.043	1.088	1.03	1.167	441
Test	Acamprosate		0.8 g	1.025	1.223	1.117	0.052	1.108	1.038	1.203	441
Test	Acamprosate		1.0 g	1.012	1.271	1.132	0.065	1.123	1.03	1.241	882
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	0.65 g	4.048	4.105	4.076	0.018	4.079	4.048	4.103	24
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	1.0 g	4.053	4.134	4.093	0.026	4.098	4.054	4.133	48
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.325 g	1.753	1.825	1.789	0.029	1.789	1.756	1.823	4
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.96 g	3.395	3.607	3.5	0.086	3.499	3.401	3.6	4
Test	Adefovir dipivoxil	~Anti-HIV~Antiviral~	0.01 g	1.022	1.106	1.064	0.042	1.064	1.026	1.102	2
Test	Adefovir	~Antiviral~	0.01 g	1.001	1.001	1.001	0.0	1.001	1.001	1.001	2
Test	Aliskiren	~Antihypertensive~	0.04 g	1.002	1.006	1.004	0.002	1.004	1.002	1.006	24
Test	Aliskiren	~Antihypertensive~	0.08 g	1.003	1.011	1.007	0.004	1.007	1.003	1.011	24
Test	Aliskiren	~Antihypertensive~	0.16 g	1.006	1.023	1.014	0.008	1.014	1.006	1.023	24
Test	Aliskiren	~Antihypertensive~	0.3 g	1.013	1.056	1.032	0.018	1.031	1.013	1.053	408
Test	Aliskiren	~Antihypertensive~	0.64 g	1.026	1.095	1.06	0.033	1.059	1.026	1.095	24
Test	Aliskiren	~Antihypertensive~	0.85 g	1.036	1.132	1.083	0.046	1.081	1.036	1.132	24
Test	Aliskiren	~Antihypertensive~	1.2 g	1.051	1.184	1.116	0.064	1.114	1.051	1.184	24
Test	Aliskiren	~Antihypertensive~	1.8 g	1.073	1.258	1.164	0.089	1.162	1.073	1.258	24
Test	Alosetron	~Antiemetic~	0.001 g	1.003	1.014	1.007	0.002	1.006	1.004	1.01	2704
Test	Alosetron	~Antiemetic~	0.002 g	1.006	1.028	1.014	0.004	1.013	1.008	1.021	2028
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	0.001 g	1	1.001	1	1.289E-4	1	1	1.001	245
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	2.5E-4 g	1	1	1	2.245E-5	1	1	1	35
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	5.0E-4 g	1	1	1	4.758E-5	1	1	1	70
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	6.3E-4 g	1	1.001	1	5.657E-5	1	1	1	35
Test	Alvimopan	~Laxative~	0.006 g	1.003	1.009	1.005	0.002	1.005	1.003	1.009	242
Test	Alvimopan	~Laxative~	0.012 g	1.005	1.019	1.011	0.004	1.01	1.006	1.017	121
Test	Alvimopan	~Laxative~	0.018 g	1.008	1.028	1.016	0.005	1.015	1.01	1.026	121
Test	Alvimopan	~Laxative~	0.024 g	1.011	1.038	1.022	0.007	1.02	1.013	1.034	121
Test	Amitriptyline	~Analgesic: non narcotic~Antidepressant~	0.025 g	1.015	1.23	1.116	0.042	1.117	1.047	1.193	1728
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.005 g	1.438	1.955	1.657	0.174	1.645	1.438	1.954	245
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.01 g	2.224	2.51	2.337	0.093	2.321	2.226	2.508	245
Test	Amoxicillin	~Antibiotic~	1.0 g	1.046	1.154	1.097	0.039	1.096	1.048	1.154	27
Test	Amprenavir	~Antiviral~	0.45 g	4.545	4.545	4.545	1.505E-5	4.545	4.545	4.545	16
Test	Amprenavir	~Antiviral~	0.6 g	4.545	4.545	4.545	1.19E-5	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	0.9 g	4.545	4.545	4.545	7.026E-6	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	1.2 g	4.545	4.545	4.545	6.297E-6	4.545	4.545	4.545	12
Test	Aprepitant	~Antiemetic~	0.08 g	0.159	0.886	0.27	0.105	0.267	0.161	0.883	4
Test	Aprepitant	~Antiemetic~	0.25 g	0.207	0.491	0.349	0.142	0.349	0.221	0.477	2
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.001 g	1	1	1	7.301E-6	1	1	1	81
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.002 g	1	1.001	1.001	2.586E-5	1.001	1	1.001	162
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.003 g	1	1.001	1.001	2.76E-4	1.001	1.001	1.001	405

Bar chart information

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

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

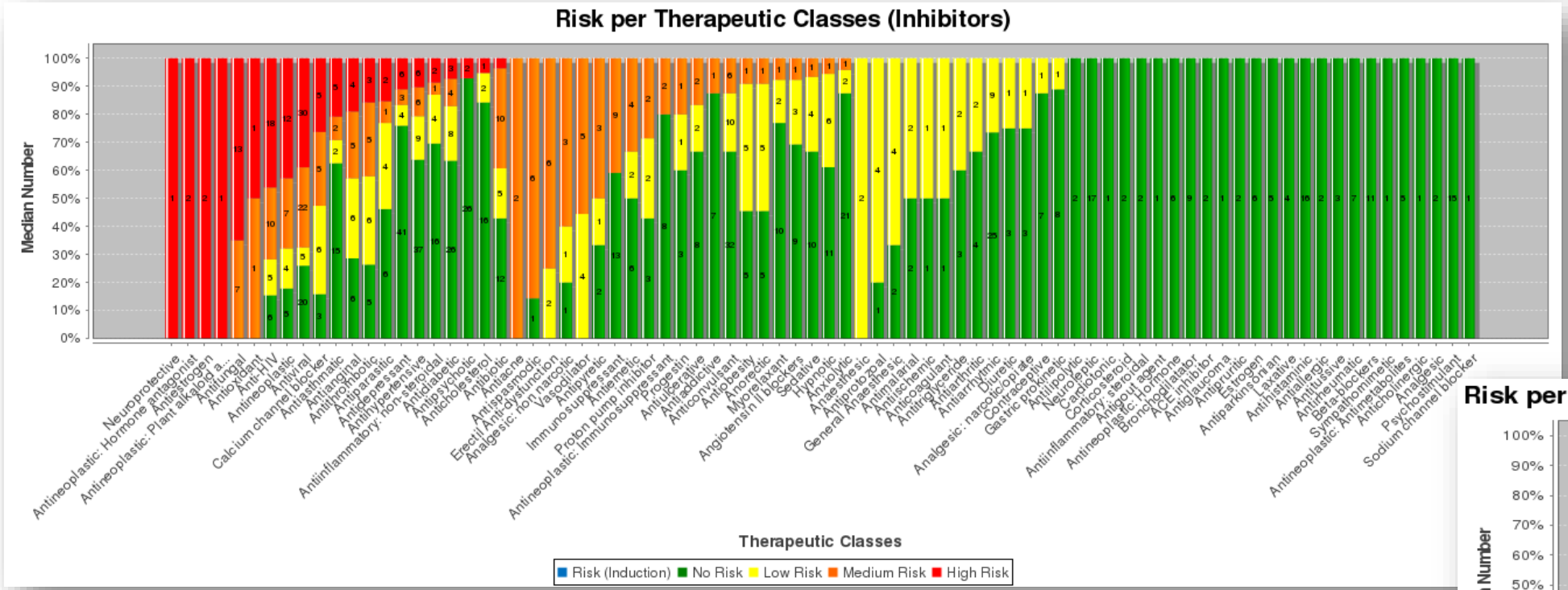
Category	*AUC ratio range*			*Colour*
Risk(Induction)		AUC ratio <	0.8	
No risk	0.8	≤ AUC ratio <	1.25	
Low risk	1.25	≤ AUC ratio <	2	
Medium risk	2	≤ AUC ratio <	5	
High risk	5	≤ AUC ratio		

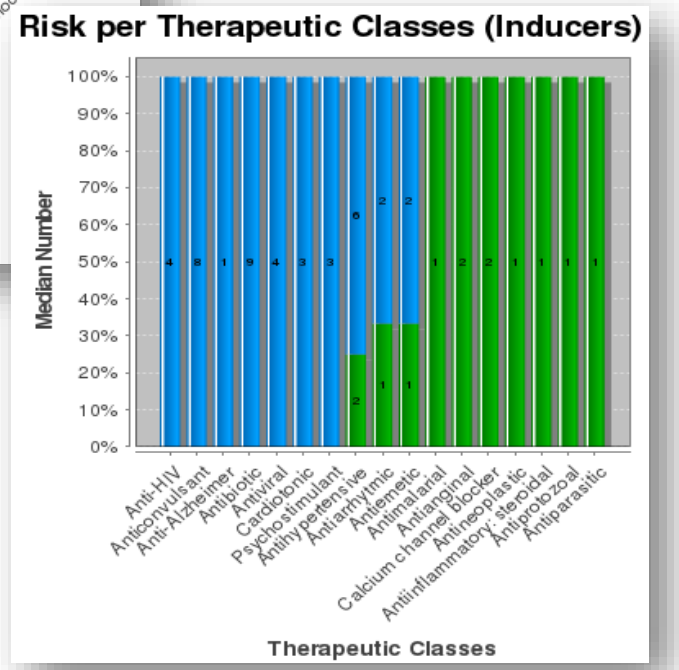
[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...

导出数据-预测结果输入的数据

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

导出结果-测试药物对每种药物分类的风险总览





drugs in tested in each class is indicated

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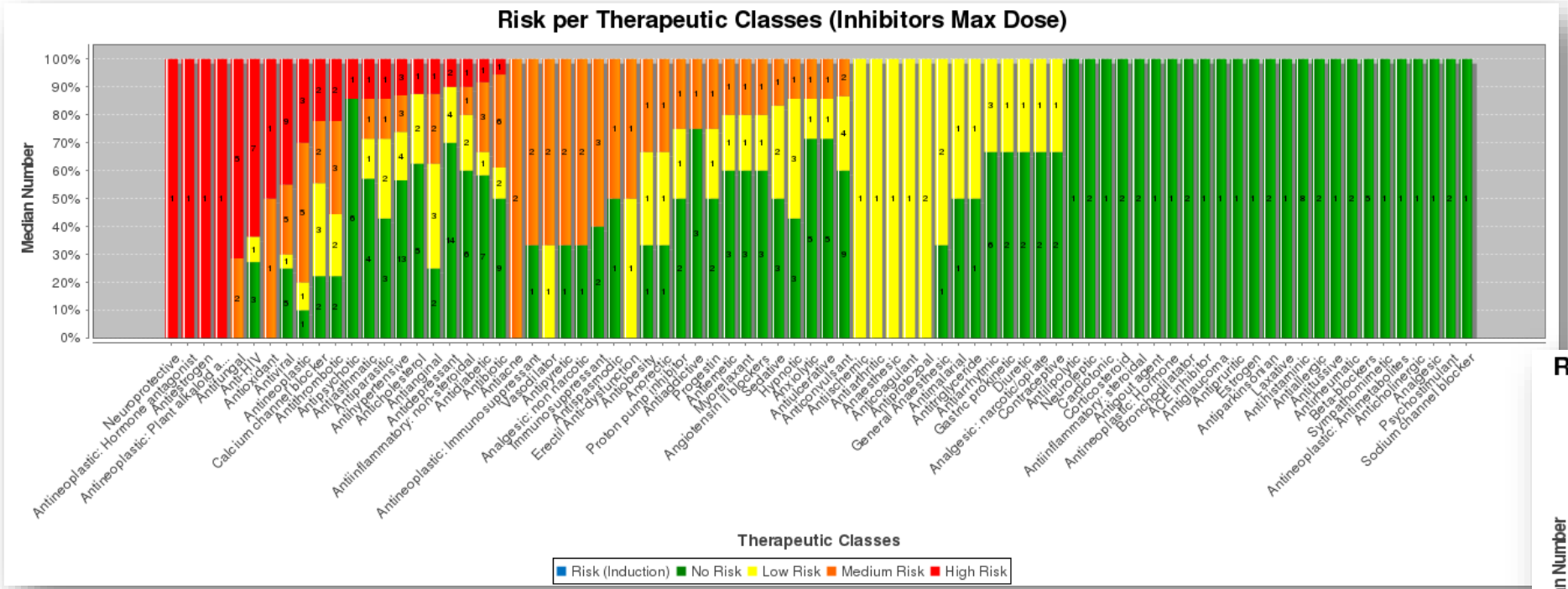
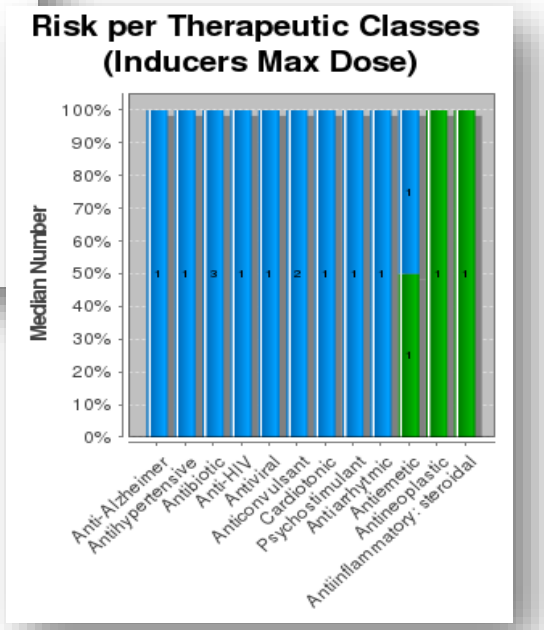
导出结果-测试药物对每种药物分类的风险总览– 最大剂量结果





drugs in tested in each class is indicated

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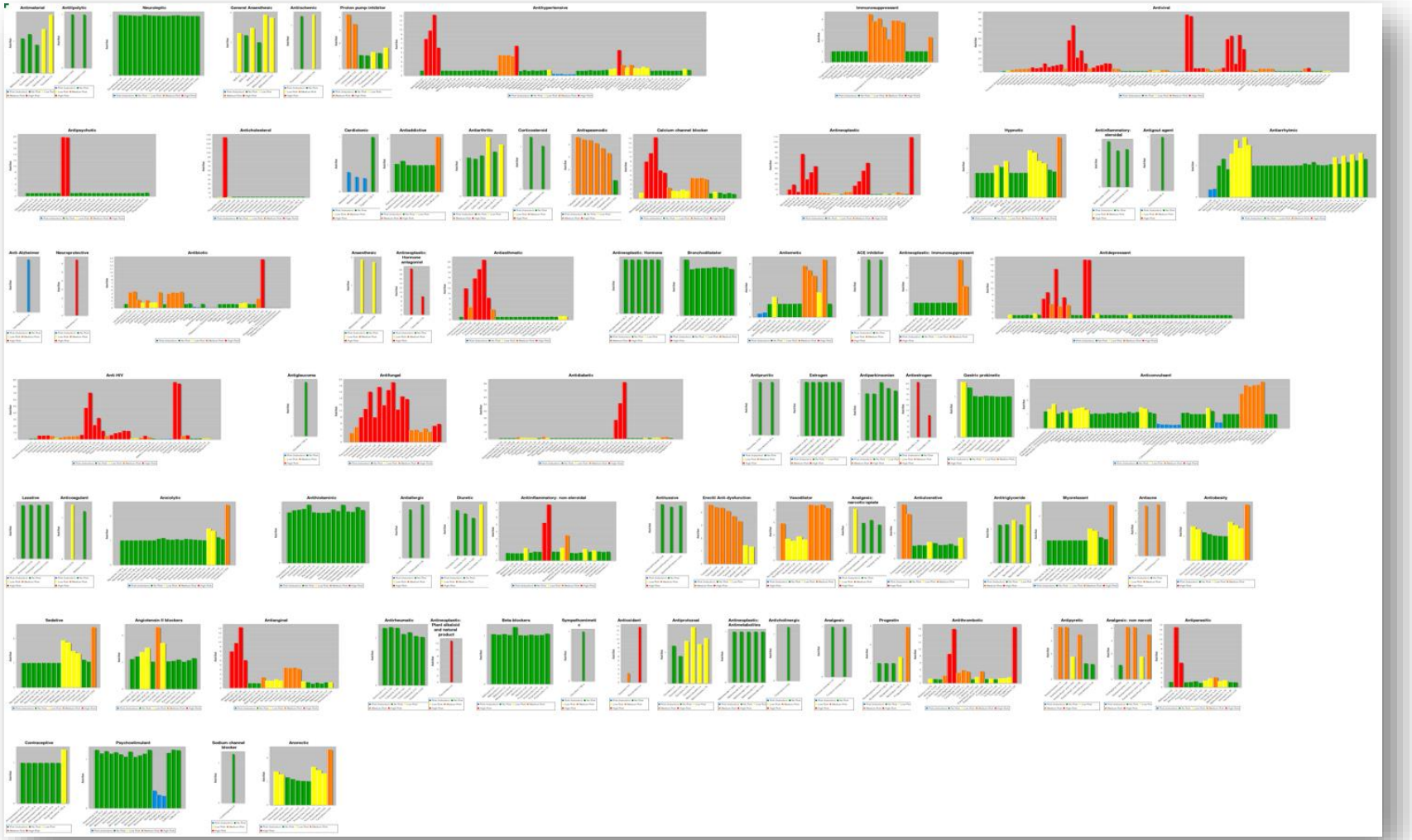
导出结果-每个药物/特定剂量下与测试药物的DDI



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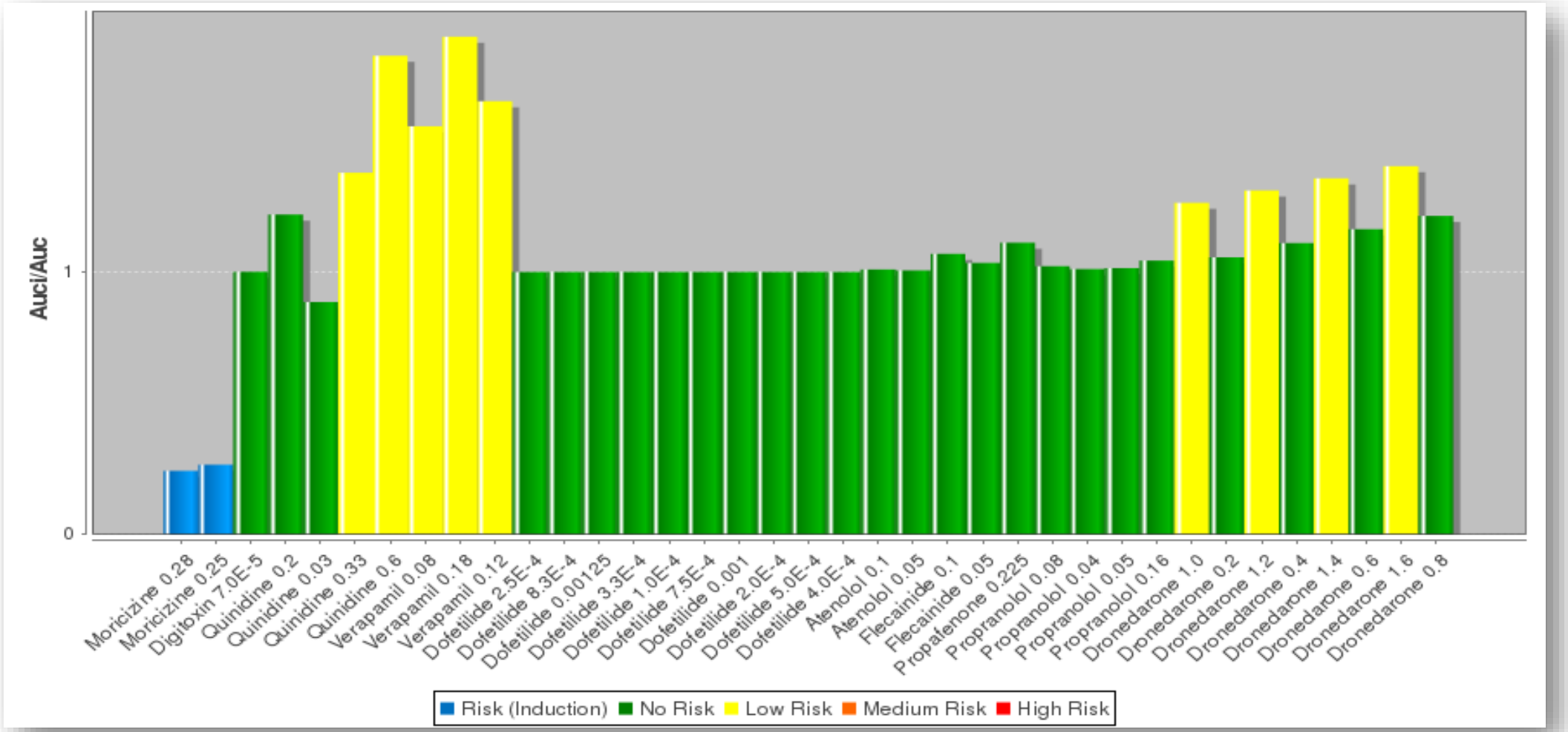
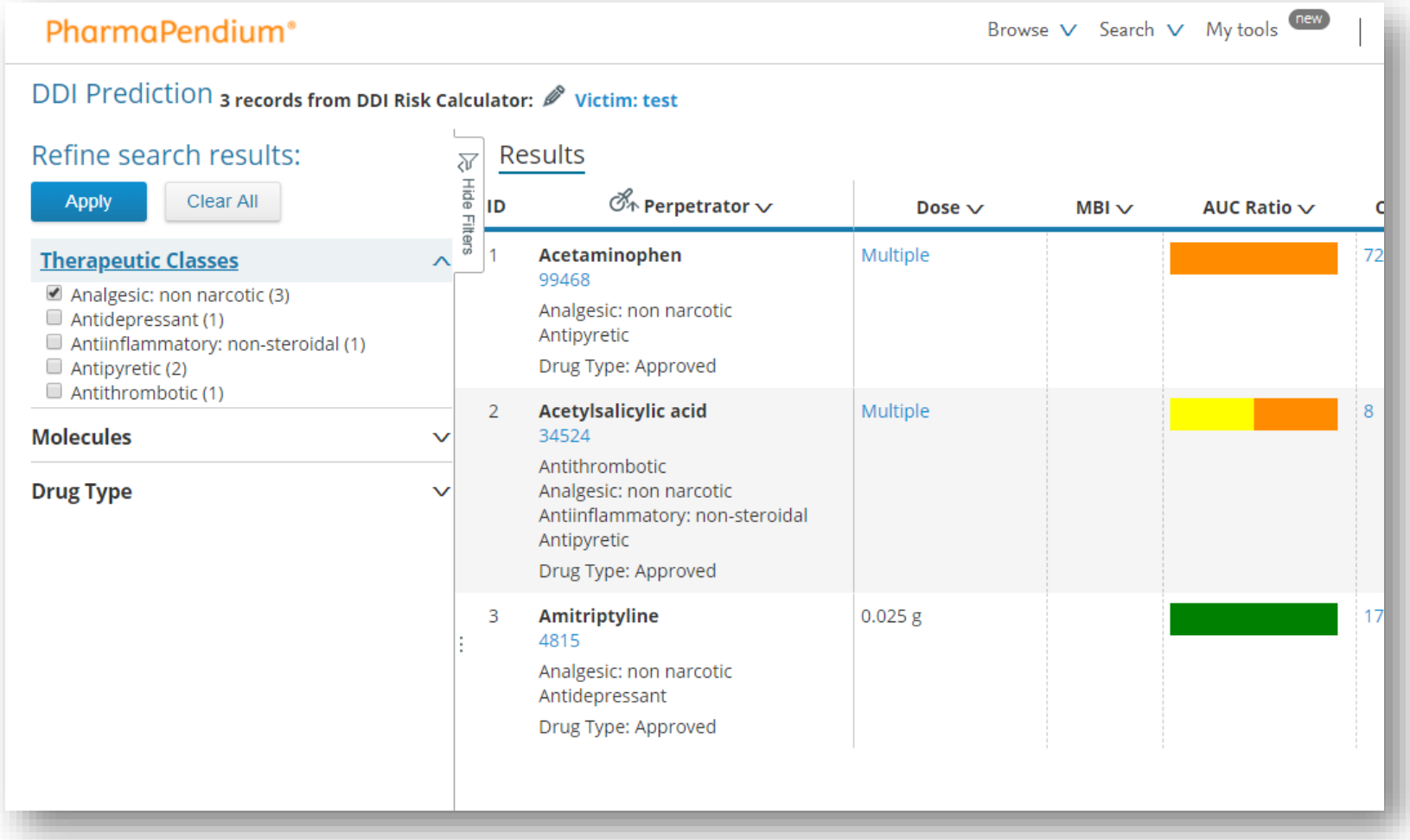
问题 – 与抗心律不齐药的潜在风险



Question: 测试化合物与对乙酰氨基酚作用风险?

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



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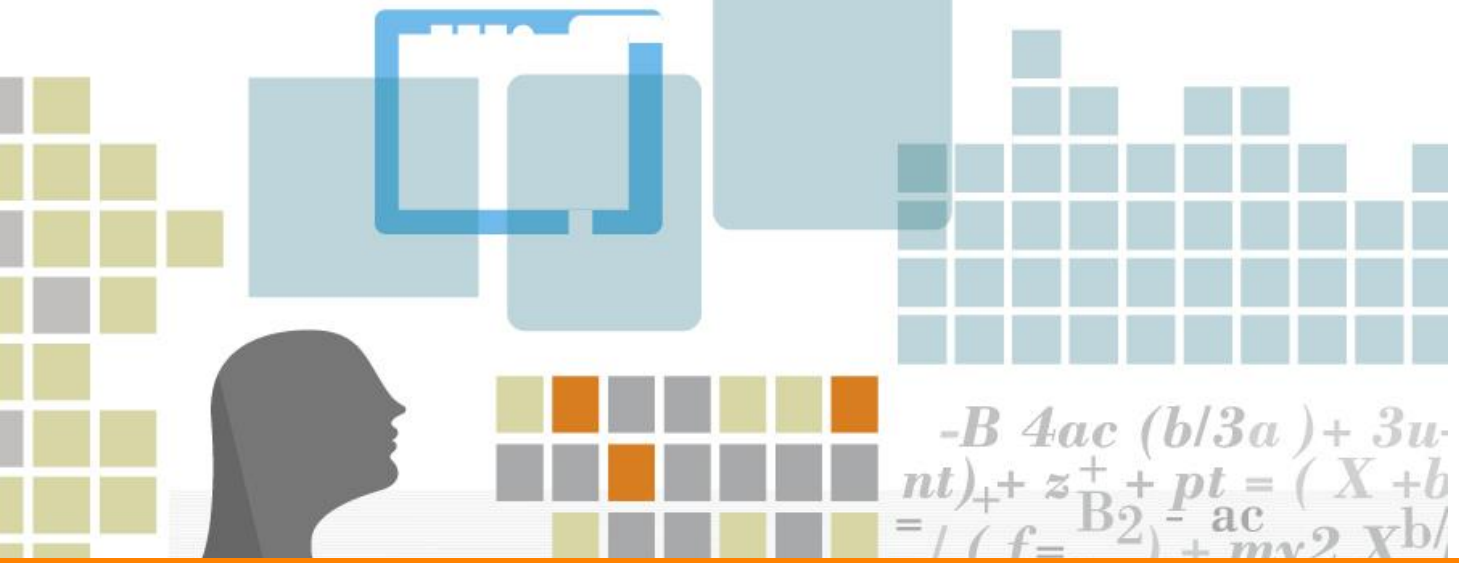
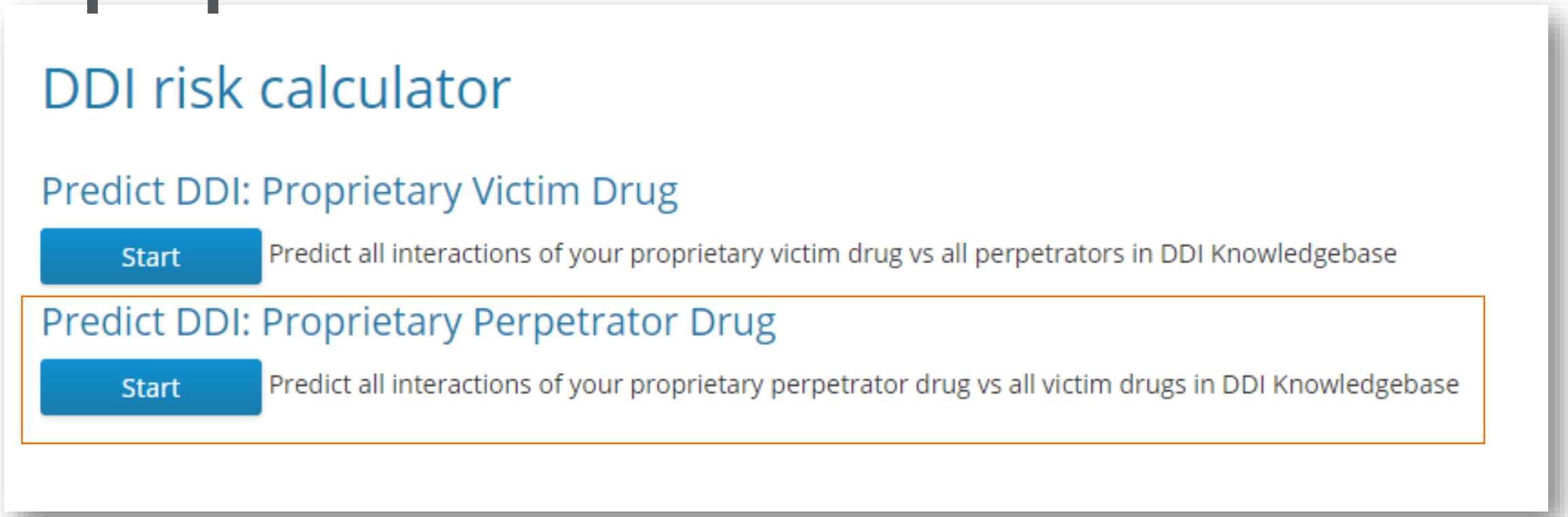
DDIRC Demo: Test compound as a perpetrator



Empowering Knowledge

Predict DDIs with the proprietary drug as a perpetrator



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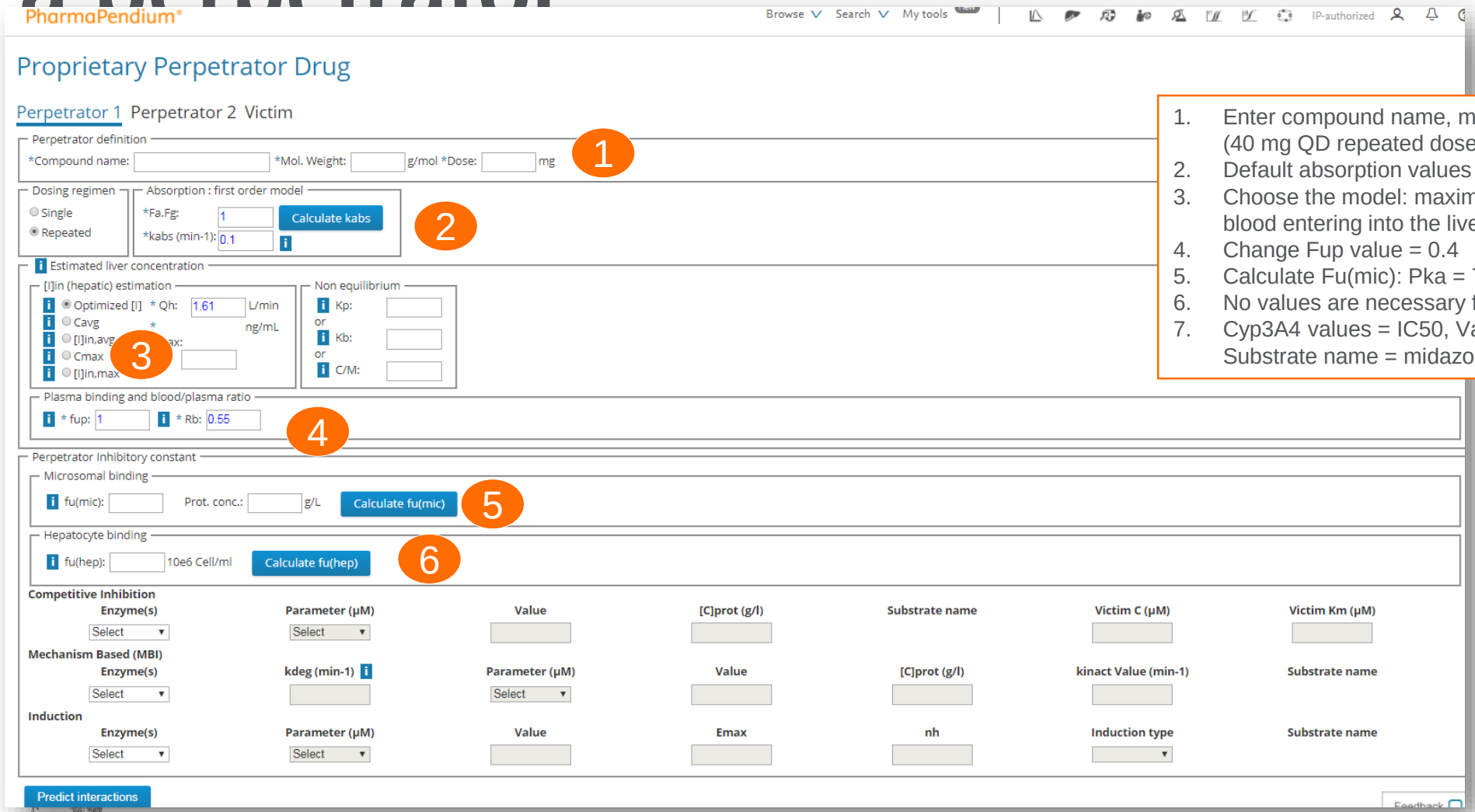
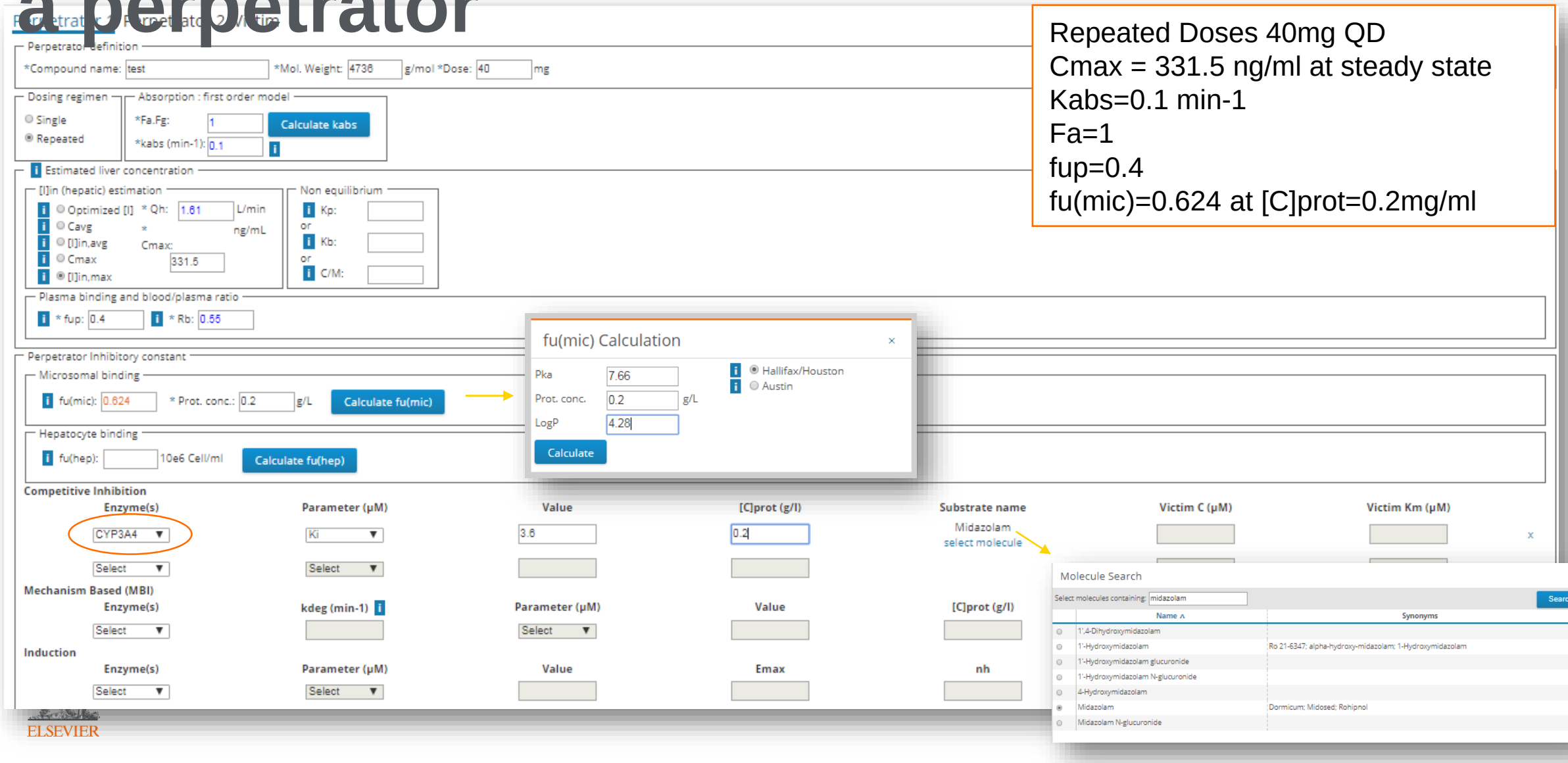
Predict DDIs with the proprietary drug as a perpetrator



1. Enter compound name, molecular weight (473.5) and dose (40 mg QD repeated dose)
2. Default absorption values are worst-case scenario (Fa=1)
3. Choose the model: maximal systemic concentration in blood entering into the liver and add Cmax (331.5 ng/ml)
4. Change Fup value = 0.4
5. Calculate Fu(mic): Pka = 7.66, [C]prot=0.2, LogP = 4.28
6. No values are necessary for hepatocyte binding
7. Cyp3A4 values = IC50, Value = 3.6, [C]prot = 0.2, Substrate name = midazolam

ELSEVIER

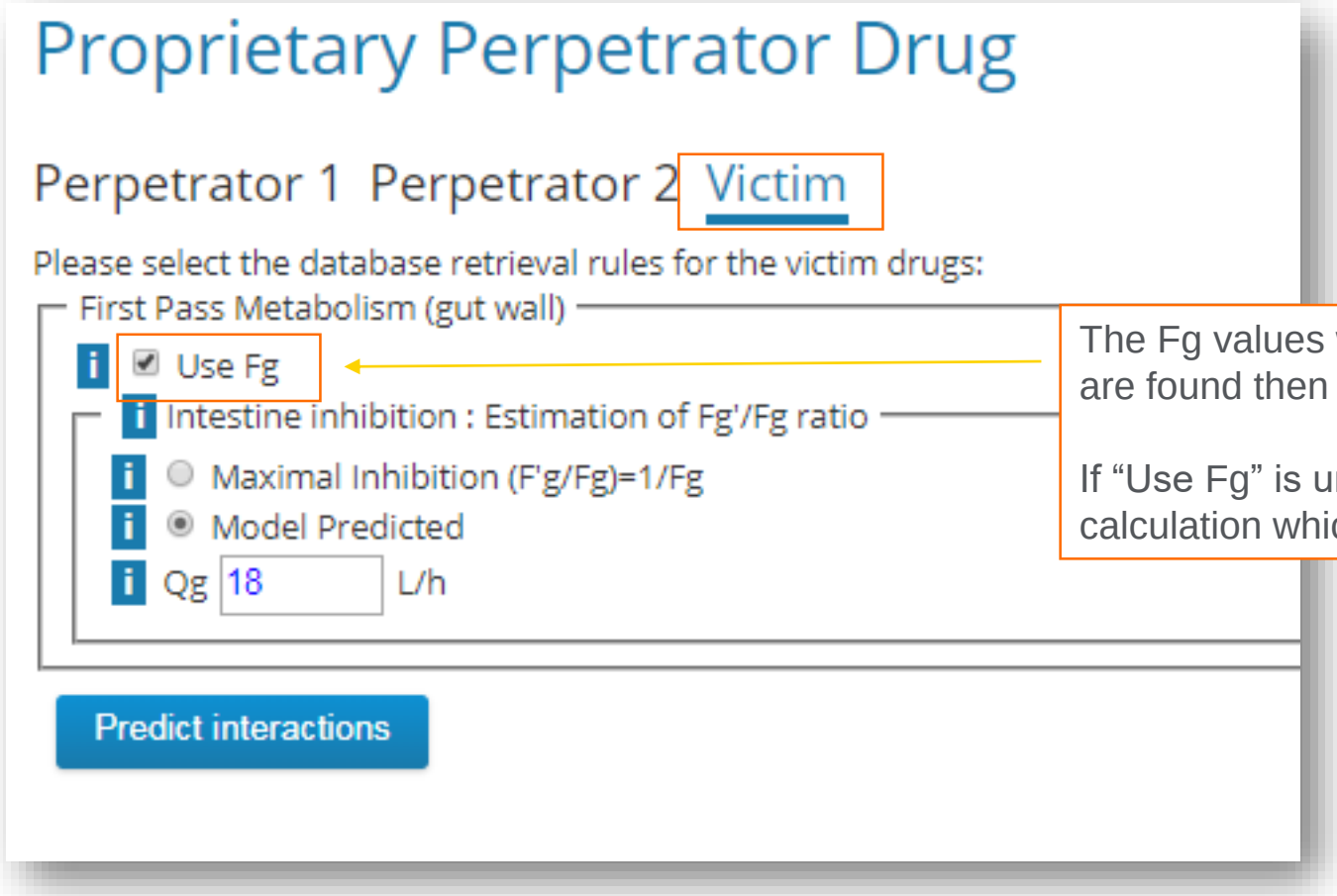
Predict DDIs with the proprietary drug as a perpetrator



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

ELSEVIER

Enter intestinal metabolism values for the Victim

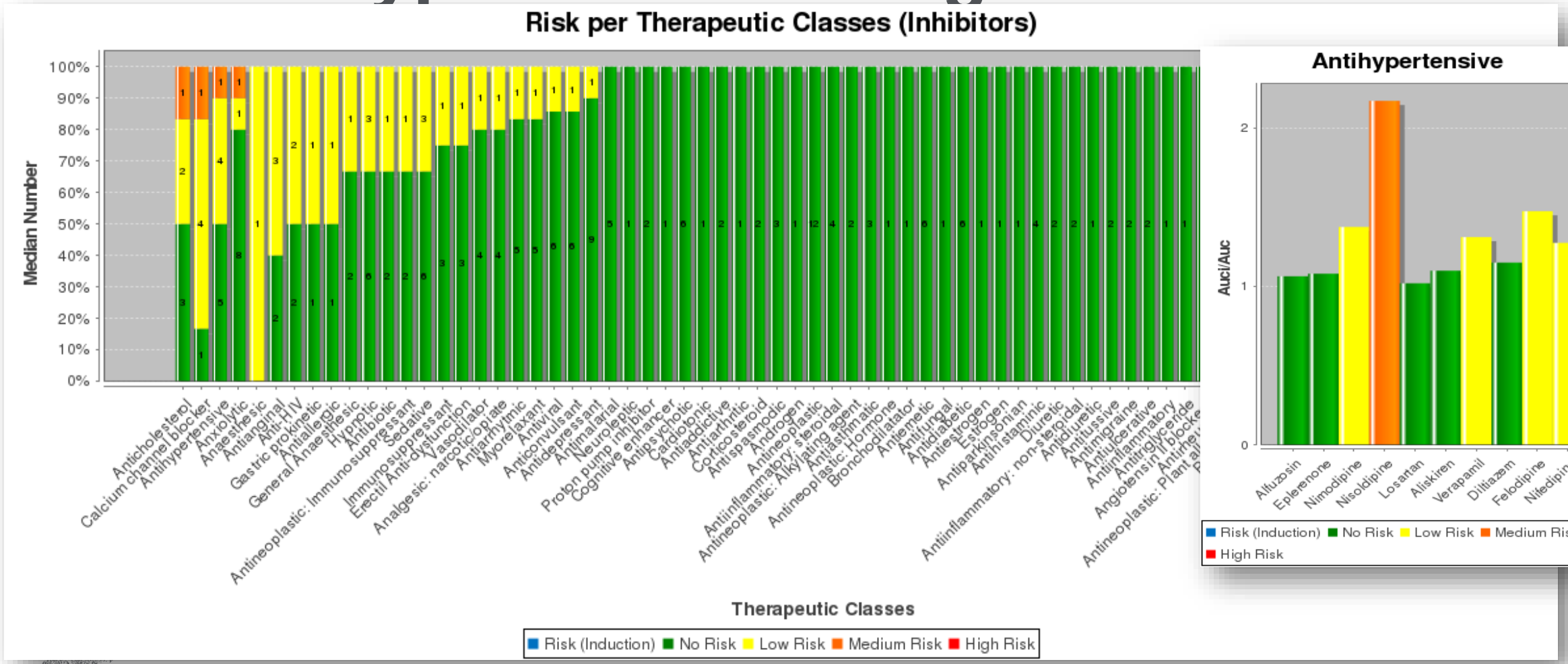


When CYP3A4 or CYP3A5 is selected, there is the option to define if & how intestinal metabolism should be taken into account.

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

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

There may be a risk with anticholesterol and antihypertensive drugs



小结

- 1. PharmaPendium运用信息分类和文本挖掘技术，对FDA/EMA的官方档案进行再处理，能够帮助用户快速获取原文关键信息，尽可能避免关键信息缺失导致的不良后果。

- 2. PharmaPendium对FDA/EMA的原文中的数据信息进行深度的提取，归类，整理，便于用户进行大数据分析，辅助实验方案制定，更好的达到实验预期，管控成本。

- 3. PharmaPendium依据FDA指南进行文本信息的整理，归拢证据，更好的与监管机构沟通，使药物审批的沟通更有效率。

Thank you