

## R&D Solutions

# Supporting Drug Safety with PharmaPendium and advanced FAERS search functionality



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# We suggest viewing the presentation in full screen





# Questions?

- You are welcome to submit questions by using the “Ask a Question” feature on your screen.
- As many questions as possible will be answered after the webinar.
- Slides and the recording will be sent to you following the webinar and are also available in the PharmaPendium Help section

**LIVE**

ASK A QUESTION RATE THIS

ASK A QUESTION CLOSE X

Enter your question for the presenter

Not hearing audio? [Click here for help](#)

Type your question here...

SEND QUESTION



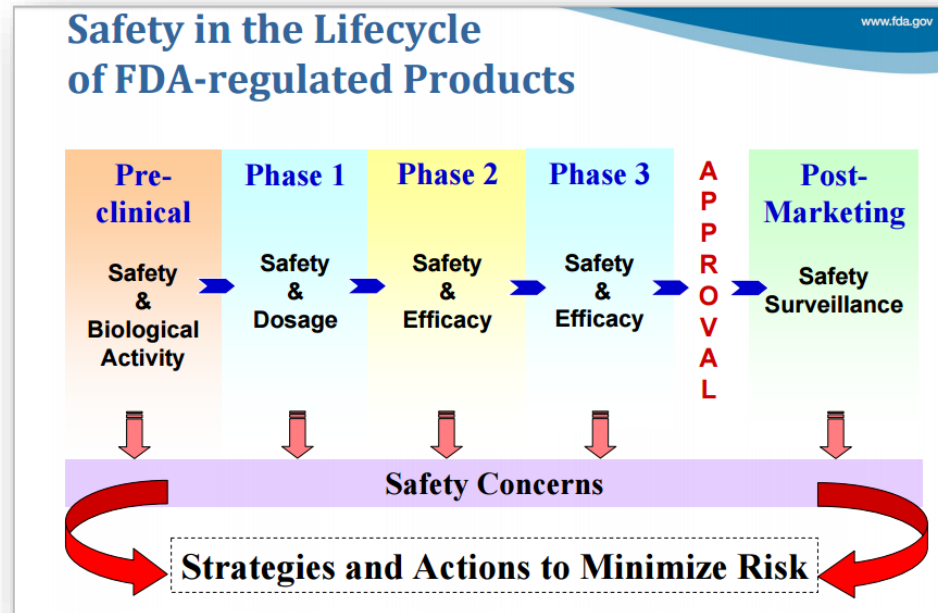
# Agenda

- Impact of Drug Safety on patient safety and drug development
- Brief PharmaPendium overview
- Sources of safety information in PharmaPendium
- Different ways to find safety information in PharmaPendium (with examples)
  - Extracted drug safety information
  - Drug-drug interactions (DDIRC and MET)
  - Post-market safety information (FAERS search)



# Drug safety is an ongoing priority

Understanding potential safety concerns begins with preclinical/toxicology assessments and continues through to post-market safety



<http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM340626.pdf>



## Types of drug safety information we will focus on

- Comparative preclinical, clinical and post-market safety information found in Drug Approval documents and literature
- Information to identify and assess the potential impact of drug-drug interactions
- Post-market safety information the FDA Adverse Event Reporting system



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



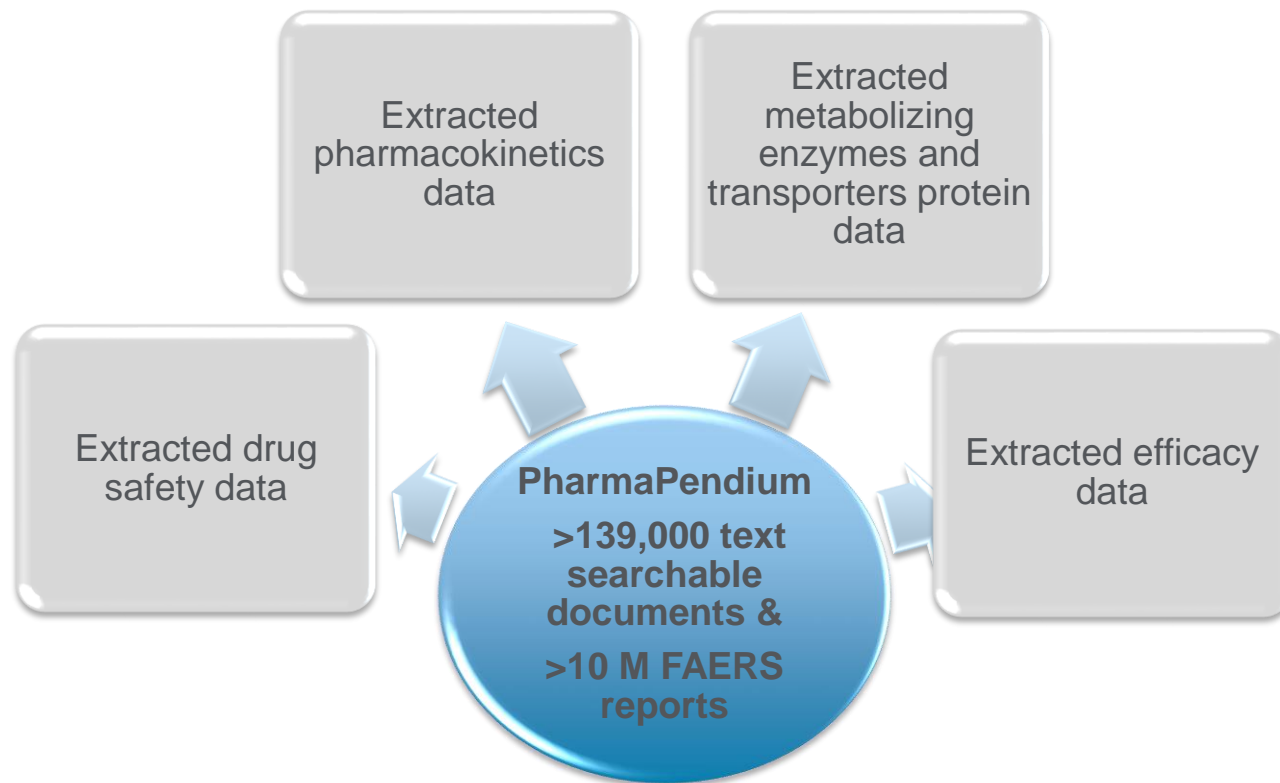
# Critical decision-support for Drug Development



- ✓ Leverage past drug approvals to inform bottleneck issues
- ✓ Design studies that provide the most meaningful data
- ✓ Reduce unnecessary preclinical and clinical costs by comparing your drug to successful ones
- ✓ Rapidly evaluate potential DDI risks



# Integrated FDA/EMA Drug Approval Docs & extracted data





# Content and value is continually growing

## Source Documents

**2.3M+**

pages of FDA  
approval  
documents

**215K+**

pages of EMA  
approval  
documents

**10.4M+**

FDA AERS  
reports

**690K+**

Pages from FDA  
Advisory  
Committee  
Meetings

## Extracted Data

**4485**

Drugs indexed  
& fully  
searchable

**1.64M+**

PK data lines

**315K+**

Metabolizing  
enzyme and  
transporter data  
lines

**1.71M+**

safety data lines

**2.71M+**

efficacy data  
lines

**115K**

activity data lines



# Drug Approval Packages

Safety information can be found throughout Drug Approval packages

Main sections with safety information:

## FDA

- Medical/Clinical Review
- Pharmacology Review
- Label/Printed Labeling

## EMA

- Assessment Report
- Marketing Authorisation Steps
- ANNEX

## FDA Approval Package



Search this FDA Package

- + Administrative documents
- + Approval Letter
- + Approval Package
- + Chemistry Review
- + Clinical Pharmacology and Bi...
- + Label
- + Letter
- + Medical/Clinical Review
- + Microbiology Review
- + Other Important Informatio...
- + Pharmacology Review
- + Printed Labeling
- + Review
- + Statistical Review
- + Summary Review

## EMA Approval Package



Search this EMA Package

- + All Authorized Presentations
- + ANNEX
- + ANNEX I
- + Assessment Report
- + Marketing Authorization Steps
- + Public Assessment Report
- + Q&A



# Searching for safety information in PharmaPendium

- Extracted safety data, Text searchable data, FAERS reports

The screenshot displays the PharmaPendium web application interface. The top navigation bar includes 'Browse', 'Search', and user status 'IP-authorized'. The main content area is titled 'Safety data search results' and shows '568 records from Safety data: Acetaminophen (568)'. On the left, a sidebar allows refining search results with filters for 'Adverse Effects / Toxicity', 'Dose Types', 'Drugs', 'Routes of Administration', 'Sources', and 'Years'. The main table lists search results with columns for ID, Drug, and Adverse Effects. A 'Browse drugs' panel on the right shows a hierarchical tree for 'paracetamol' (Acetaminophen), including categories like Analgesics, Antipyretics, and Analgesics, non-narcotic. Below this, the 'Adverse Effects / Toxicity\*' section provides a detailed view of safety data, including a table of adverse effects and their frequencies across Preclinical, Clinical, and Post-Marketing data.

**PharmaPendium®** Browse Search | IP-authorized

Safety data search results 568 records from Safety data: Acetaminophen (568)

Refine search results: Apply Clear All

Preclinical Data Clinical Data

Adverse Effects / Toxicity

Dose Types

Drugs

Routes of Administration

Sources

Years

ID Drug Adverse Effects

ID	Drug	Adverse Effects
1	Acetaminophen	Muscle spasms
2	Acetaminophen	Hypophosphatemia
3	Acetaminophen	Aspartate aminotransferase
4	Acetaminophen	Hepatocellular
5	Acetaminophen	Injection site
6	Acetaminophen	Muscle spasms
7	Acetaminophen	Rash

**PharmaPendium®** Browse Search | IP-authorized

Browse drugs

paracetamol

- Analgesics
  - Analgesics, non-narcotic
    - Acetaminophen
- Antipyretics
  - Acetaminophen

Browse drugs - Analgesics > Analgesics, non-narcotic

Acetaminophen

Fever  
Headache tension  
Pain mild

Adverse Effects / Toxicity\*:

Viewing by area affected View by name

	Preclinical Data view all 1364	Clinical Data view all 568	Post-Marketing Reports (AERS) view all 37142
+ Blood and lymphatic system disorders	33	19	1400
+ Cardiac disorders	3	14	2340
+ Congenital, familial and genetic disorders	12	4	143
+ Ear and labyrinth disorders	1	no data	255
+ Endocrine disorders	10	no data	39
+ Eye disorders	5	no data	765
+ Gastrointestinal disorders	12	72	7123
+ General disorders and administration site conditions	145	47	10609
+ Hepatobiliary disorders	304	25	6632
+ Immune system disorders	5	12	1194

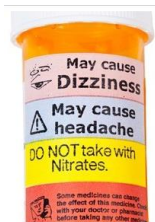


# Search using a wide range of Drug Safety parameters

## Adverse Events/Toxicity

### AE taxonomy

- Normalized to MedDRA
- Unique translational view of AEs across preclinical, clinical and post-market



## Species

### Includes:

- Human
- Vertebrates
  - Birds
  - Fish
  - Mammals



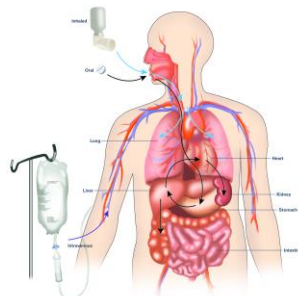
## Dose, dose types

### Includes:

- Extracted dose data
- Single/repeated dose



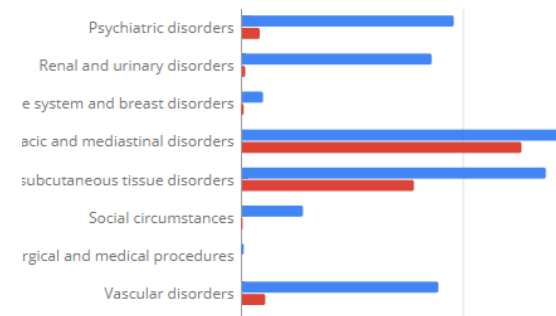
## Route of administration



## Post-market data – also searchable using the FAERS Search form

### Includes:

- Drug role (primary, secondary, concomitant, interacting)
- Outcome (serious/non-serious)
- Age/gender
- Reporter occupation
- Route of administration
- Drug manufacturer





# Sources of extracted preclinical safety data

Refine search results:

[Apply](#) [Clear All](#)

**Adverse Effects / Toxicity** ▼

**Dose Types** ▼

**Drugs** ▼

**Routes of Administration** ▼

**Sources** ▲

- ☐ FDA approval packages (375)
  - ☐ Label (2)
  - ☐ Pharmacology Review (373)
- ☐ PharmaPendium Published Toxicity (989)

**Species** ▼

**Years** ▼

PharmaPendium®

Browse ▾ Search ▾ | IP-authorized

Safety data search results 1364 records from Safety data: Acetaminophen (1364)

[Show/hide columns](#) [Show drugs in...](#) [Export](#)

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

ID	Drug	Species	Dose	Dose Type	Route	Source	Year
1	Acetaminophen		640 mg/kg	Single	Oral	PharmaPendium Published Toxicity: Toxicology International 2011; 18:140 <a href="#">Locate Article</a>	2011
2	Acetaminophen		50 mg/kg/day	Repeated	Intravenous	FDA approval package document: Pharmacology Review (Page:39) PDF 19675k	2012
3	Acetaminophen		50 mg/kg/day	Repeated	Intravenous	FDA approval package document: Pharmacology Review (Page:36) PDF 19675k	2012
4	Acetaminophen		450 mg/kg	Single	Intraperitoneal	PharmaPendium Published Toxicity: Journal of Biological Chemistry 2013; 288:15342 <a href="#">Locate Article</a>	2013
5	Acetaminophen		530 mg/kg	Single	Intraperitoneal	PharmaPendium Published Toxicity: Toxicology and Applied Pharmacology 2011; 257:449 <a href="#">Locate Article</a>	2011
6	Acetaminophen		300 mg/kg	Single	Intraperitoneal	PharmaPendium Published Toxicity: Hepatology 2013; 58:2099 <a href="#">Locate Article</a>	2013
7	Acetaminophen		500 mg/kg	Single	Intraperitoneal	PharmaPendium Published Toxicity: Journal of Experimental and Integrative Medicine 2015; 5:16 <a href="#">Locate Article</a>	2015
8	Acetaminophen	Wistar-Kyoto monkey	900 mg/kg, 14D	Repeated	Intragastric	PharmaPendium Published Toxicity:	2015



# Sources of extracted clinical safety data

Refine search results:

[Apply](#) [Clear All](#)

**Adverse Effects / Toxicity** Hide Filters

**Dose Types** Hide Filters

**Drugs** Hide Filters

**Routes of Administration** Hide Filters

**Sources** Hide Filters

- ☐ FDA approval packages (526)
  - ☐ Label (66)
  - ☐ Medical/Clinical Review (456)
  - ☐ Pharmacology Review (4)
- ☐ Meyler's (27)
- ☐ Mosby's Drug Consult™ (6)
- ☐ PharmaPendium Published Toxicity (9)

**Years** Hide Filters

PharmaPendium®

Browse Search | IP-authorized

Safety data search results 568 records from Safety data: [Acetaminophen \(568\)](#)

[Show/hide columns](#) [Show drugs in...](#) [Export](#)

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

ID	Drug	Species	Dose	Dose Type	Route	Source	Year
1	Acetaminophen		1000 mg/every 6 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:53) PDF 1839k	2009
2	Acetaminophen		15 mg/kg/every 6 hours or 12.5 mg/kg/every 4 hours	Repeated	Intravenous	FDA approval package document: Label (Page:6) PDF 832k	2010
3	Acetaminophen		10-15 mg/kg/every 4-8 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:39) PDF 2564k	2009
4	Acetaminophen		Therapeutic	Repeated		Meyler's: Paracetamol, Acetaminophen	2006
5	Acetaminophen		10-15 mg/kg/every 4-6 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:75) PDF 1839k	2009
6	Acetaminophen		10-15 mg/kg/every 4-8 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:33) PDF 2564k	2009
7	Acetaminophen		15 mg/kg/every 6 hours or 12.5 mg/kg/every 4 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:14) PDF 945k	2009
8	Acetaminophen		10-15 mg/kg/every 4-8 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:37) PDF 2564k	2009
9	Acetaminophen		1000 mg/every 6 hours or 650 mg/every 4 hours	Repeated	Intravenous	FDA approval package document: Medical/Clinical Review (Page:51) PDF 1839k	2009



# Sources of extracted post-market safety data

**PharmaPendium®** Browse Search | IP-authorized

Safety data search results 148048 records from Safety data: Adrenergic agonists (148048)

Refine search results:  
Apply Clear All

Adverse Effects / Toxicity  
Drugs  
Sex  
Serious/Non-serious

PharmaPendium post market reports are taken from the FDA AERS database.  
This database is used as provided by the FDA CDER in PharmaPendium and may contain duplicate records, coding and classification errors.

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

ID	Drug	# Reports	Adverse Events	Reports by Gender
1	Acetaminophen; Chlorpheniramine Maleate; Dextromethorphan Hydrobromide; Phenylephrine Hydrochloride	75	Blood glucose increased (8) Hypersensitivity (8) Dizziness (7) Swelling face (7) Choking (6) Wrong technique in drug usage process (6) Diabetes mellitus (5) Drug ineffective (4) Dyspnoea (4) Headache (4) view all ...	Female (46) Male (27)
2	Acetaminophen; Dichloralphenazone; Isometheptene Mucate	68	Pharmaceutical product complaint (10) Headache (8) Chest pain (7) Drug ineffective (6) Palpitations (6) Dizziness (5) Hypotension (5) Restlessness (5) Somnolence (5) Tachycardia (5) view all ...	Female (51) Male (11)
3	Aclidinium Bromide; Formoterol Fumarate Dihydrate	2	Dysphagia (1) Dyspnoea (1) Hypersensitivity (1) Pneumonia (1) Pulmonary oedema (1)	Female (1) Male (1)
4	Albuterol	7203	Pharmaceutical product complaint (1675) Drug ineffective (1424) Dyspnoea (1221) Asthma (987)	Female (3800) Male (2548)



# Text-searchable safety information in PharmaPendium

The screenshot displays the PharmaPendium search interface. At the top, a 'Quick search' bar contains the query 'paracetamol AND nausea' and a 'Search' button. Below this, the main search results page is shown, featuring a sidebar with filters for 'Drugs', 'Sources', and 'Years'. The search results list several documents, including a 'Drug monograph for Acetaminophen' and an 'Approval Package 019833 Part 01 PDF 2758k'. A detailed view of the 'FDA Approval Package' is shown on the right, displaying the 'Clinical Pharmacology and Biopharmaceutics Review' for 'Liraglutide'. The review text discusses the relationship between plasma exposure and nausea events, mentioning that there was no clear relationship for moderate-severe nausea events (Figures 14 and 15). The interface also includes a 'Jump to: page 1' option and a 'Hide Filters' button.

Quick search

All These Sources  Search

☒ Include synonyms

PharmaPendium®

Search results 4785 records from Documents: paracetamol AND nausea with synonyms [QUERY]

Refine search results:

Apply Clear All

Drugs

Sources

Years

Jump to: page 1

Document with context

1 Drug monograph for Acetaminophen

2 Briefing 4411 Part 06 (Anesthetic and Analgesic Drug Products Committee) PDF 2969k

3 Slides 3882 Part 04 (Nonprescription Drugs Advisory Committee) PDF 2969k

4 Approval Package 019833 Part 01 PDF 2758k

5 Clinical Pharmacology and Biopharmaceutics Review 206321/5 PDF 944k

6 Chlorzoxazone

7 Codeine

PharmaPendium®

FDA Approval Package

Search this FDA Package

- + Administrative documents
- + Approval Letter
- + Chemistry Review
- Clinical Pharmacology and Biopharmaceutics Review
  - 2014-02-26 PDF(944k) Clinical Pharmacology a...
  - 2014-02-26 PDF(4929k) Clinical Pharmacology a...
  - 2014-02-26 PDF(2344k) Clinical Pharmacology a...
  - 2009-11-04 PDF(5698k) Clinical Pharmacology a...
  - 2009-11-04 PDF(6017k) Clinical Pharmacology a...
  - 2009-11-04 PDF(6780k) Clinical Pharmacology a...
- + Label
- + Letter
- + Medical/Clinical Review
- + Medication Guide
- + Microbiology Review
- + Other Important Information...
- + Pharmacology Review
- + Review
- + Statistical Review

FDA Approval Package - Liraglutide > Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review 206321/5-000 Part 02

were of special interest, for example, pancreatitis, gallbladder disorders, neoplasms, thyroid disease, acute renal failure, allergic reactions, injection site reactions, cardiovascular disorders, and psychiatric disorders. For detailed review on these safety issues, please see clinical review. This review will focus on whether there were any exposure-response relationships for some of these adverse events of interest.

At the request of the FDA, the sponsor conducted time to event and exposure-response analysis for gastrointestinal (GI) adverse events (such as **nausea** and vomiting) and hypoglycemia. The analysis was done using data from trials 1807, 1922 and 1839 individually and then pooled. The patients included for the exposure-response analyses were those with a concentration value during maintenance treatment. The multivariate analyses for **nausea** and vomiting included covariates: gender, baseline body weight, and the pre-diabetes status at screening. The pooled analyses also include trial as a covariate. In trial 1922 all patients had diabetes thus the inclusion of pre-diabetes status in the model had no impact.

**Nausea and vomiting:** The results showed that there was a relationship between plasma exposure and nausea (any grade, any time). However, there was no clear relationship for moderate-severe nausea events (Figures 14 and 15). Similarly, there was a relationship with vomiting at any time and any grade but not for moderate-severe events (Figures 16 and 17). Time to event analysis did not indicate any relationship between exposure and an increased risk of events over time. Most of the **nausea** and vomiting events were of mild category and occurred early, within the first three months of treatment.

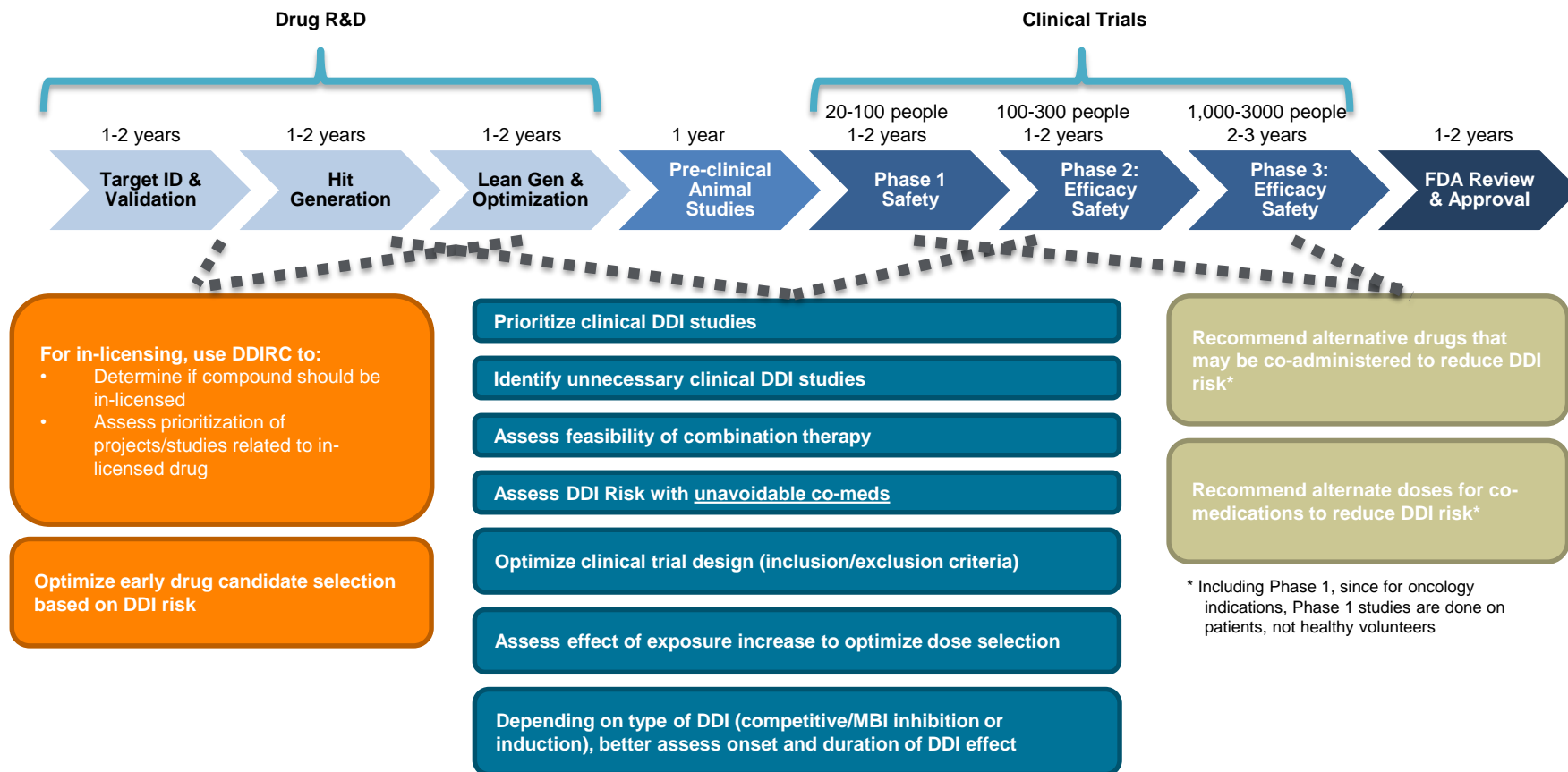
1 of 13



# Demo 1: Search extracted safety information



# Accurate prediction of DDIs informs key decisions

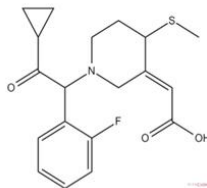




# Search using a wide range of MET parameters

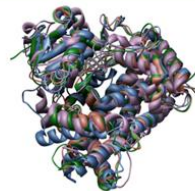
## Metabolites

Created, when available

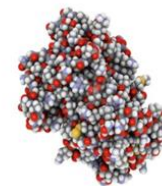


## CYPs

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

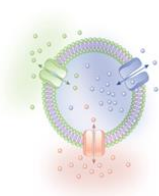


## Phase 2 Enzymes



## Transporters

And drug effects on transporters



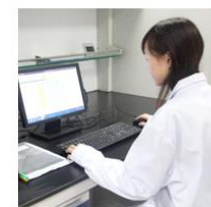
## In Vitro

**Dynamic parameters** such as CL<sub>int</sub> (Intrinsic Clearance) and K<sub>m</sub> (Michaelis Constant), V<sub>max</sub> (Maximum rate of reaction)



## DDI Studies

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



All with drug as: **Substrate, inducer or inhibitor**



## Demo 2 – predict DDIs (DDIRC and MET)



# Spontaneous reporting databases

VigiBase	EudraVigilance	FAERS
<p><b>Organization:</b> The World Health Organization for International Drug Monitoring</p> <p><b>Established:</b> 1968</p> <p><b>Number of records:</b> &gt;14 million individual case safety reports (ICSR) from 110 participating countries.</p> <p><b>Type of data:</b> ICSRs of post-marketing spontaneous serious and non-serious cases. Case reports from studies, clinical trials, special monitoring and literature are sometimes included. Data accessible only to authorized representatives of member countries.</p>	<p><b>Organization:</b> European Medicines Agency</p> <p><b>Established:</b> 2001</p> <p><b>Number of records:</b> &gt;9.5 million adverse reaction reports referring to &gt;6 million individual cases</p> <p><b>Type of data:</b> ICSRs reported by national medicine authorities and MAH. The EMA publishes regular summaries of suspected adverse drug reactions, but national competent authorities are responsible for regular review and analysis of safety signals from the database.</p>	<p><b>Organization:</b> The United States Food Drug Administration (FDA)</p> <p><b>Established:</b> 1969</p> <p><b>Number of records:</b> &gt;9 million reports</p> <p><b>Type of data:</b> Contains information on adverse events and medication error reports submitted to the FDA by consumers, health practitioners and drug manufacturers.</p>
<p>VigiBase and EudraVigilance collect ICSRs that MAHs and Competent Authorities of member countries are required to submit upon notification of a possible adverse event. The adverse event may come to their attention through spontaneous reporting by consumers and healthcare professionals, mandatory reporting from clinical trials and structured post-marketing surveillance programs, medical literature, monitored internet sites, and more. ICSR refers to the format and content for the reporting. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product.</p>		<p>FAERS includes mandatory reports of adverse events from drug manufacturers, distributors and other stakeholders as ICSRs. The database also includes voluntary reporting on adverse events or medication errors from healthcare professionals and consumers.</p>



# Perform comparative or direct FAERS searches

## Summary Table and Graphical View <sup>new</sup>

- ☒ Select drugs of interest
- ☐ Select adverse effects (AEs) of interest

Start

This new search type enables more advanced queries of FAERS reports.

Options include viewing FAERS reports:

- Based on a group of drugs (applying logic operators AND/OR/NOT)
- With comparative view of drugs in a summary table (e.g., view FAERS reports for a drug versus another drug),
- With a graphical representation of the FAERS reports.
- All types of searches include advanced filtering options (e.g., by reporter occupation, age, gender, etc.)

## Direct FAERS search

Start

Retrieve information on drugs and adverse events from FAERS reports and filter results by drug role, serious vs not serious outcome, type of adverse event and age/gender of patient. Use this page to directly accessing the FAERS reports from a simple query.

Example searches include:

- "Show me all FAERS reports where my drug has been reported"
- "Show me all reports where my drug is reported as a primary and secondary suspect drug"
- "Show me all reports where patients are taking only my drug of interest with no other co-medications"

### **NEW – choose this search to:**

- Compare and visualize AEs reported for a drug or group of drugs
- Build your own drug groups (e.g., with/without a drug, by role [primary vs secondary suspect], etc.)
- Apply filters (e.g., reporter occupation) to compare AEs reported for a drug/drug group

### **Choose this search to:**

- Look for AEs reported for a drug, drug class or by indication and to access FAERS reports directly
- Search for reports of drugs in any role
- Filter for co-medications of interest
- Apply filters (e.g., seriousness of outcome, age and date) to narrow down results
- See details from reports in tabular form and export results for further analysis



## FAERS searching lets you quickly compare safety data

- ✓ Compare the number of FAERS reports for a drug versus drug class
- ✓ View drugs reported as a primary or secondary suspect drug
- ✓ Look up FAERS reports related to a particular therapy where patients may be on multiple drugs, irrespective of the drugs' reported role
- ✓ Compare the adverse effect profile across drugs that belong to the same drug class
- ✓ Compare the adverse effect profile across demographic characteristics such as age and gender
- ✓ View reports where Drug A is reported but not Drug B
- ✓ Filter/segment the reports based on (e.g.,) who has filed the report or by route of administration



# Demo 3: Leveraging FAERS to identify safety concerns



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**Thank You!**  
**Any Questions?**

For more information:

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