OpenVigilFDA – Tutorial

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1. Introduction

OpenVigilFDA is a web-based user interface to the FDA Adverse Event Reporting System (AERS) database for extraction and analysis of drug/adverse event safety reports using the **openFDA** online-API. This data is helpful for generating hypotheses for new adverse drug reactions, drug-drug-interactions and safety comparisons. openFDA aims at providing a clean and curated access to the underlying AERS database and can count reports stratified to an extraction condition. Results are used for statistics and reported to the user via HTML or several other outputs.

2. Technical issues

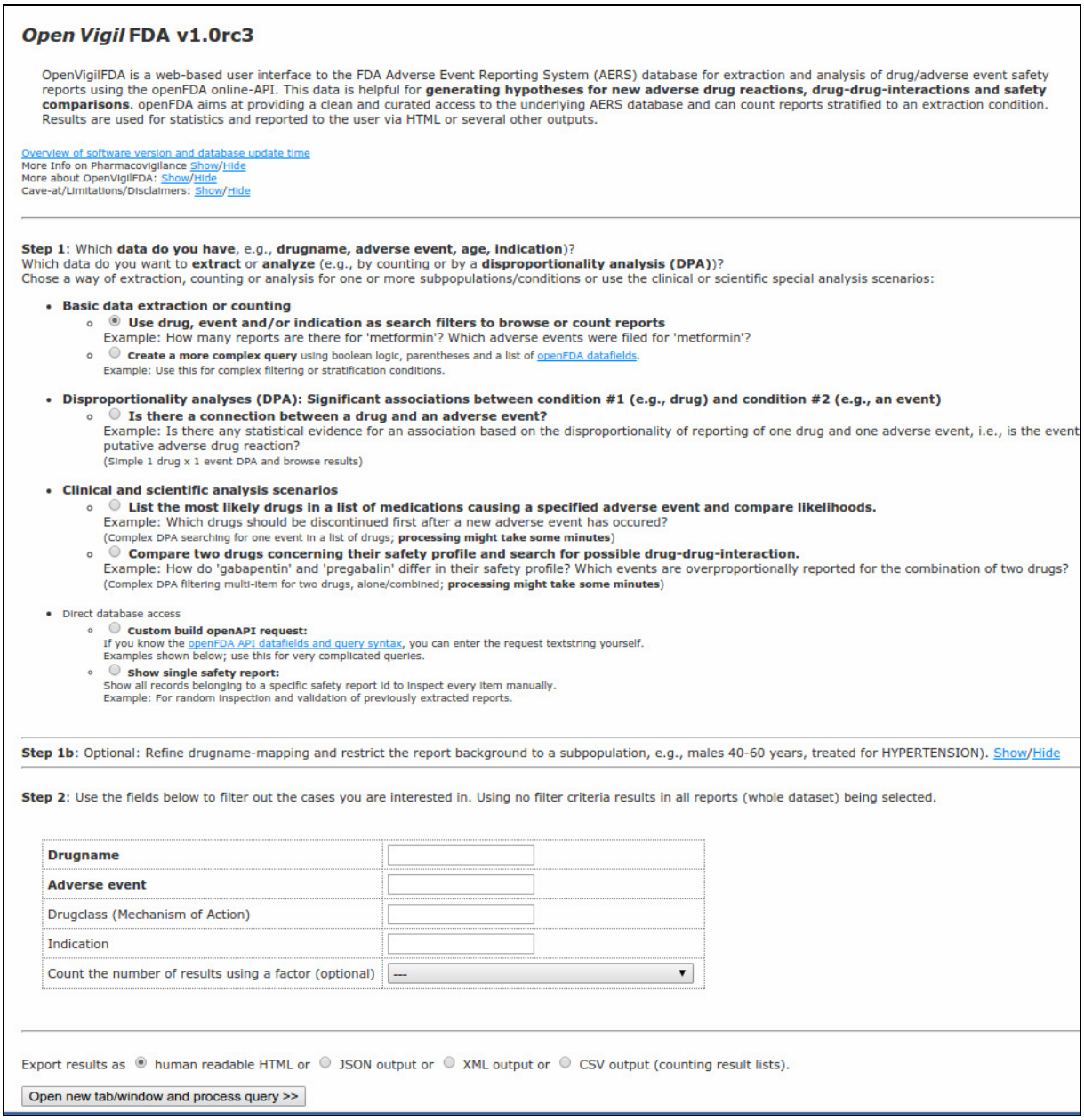
openFDA has some technical limitations, e.g., lists are truncated after 100 items, or extracting more than 5000 reports per query is not possible. This affects mostly disproportionality analyses (DPA) and any attempts to group and count results (limit 100 results). Some results will thus be incomplete. OpenVigil 2 is thus recommended for analyses of small numbers.

3. Data cleaning

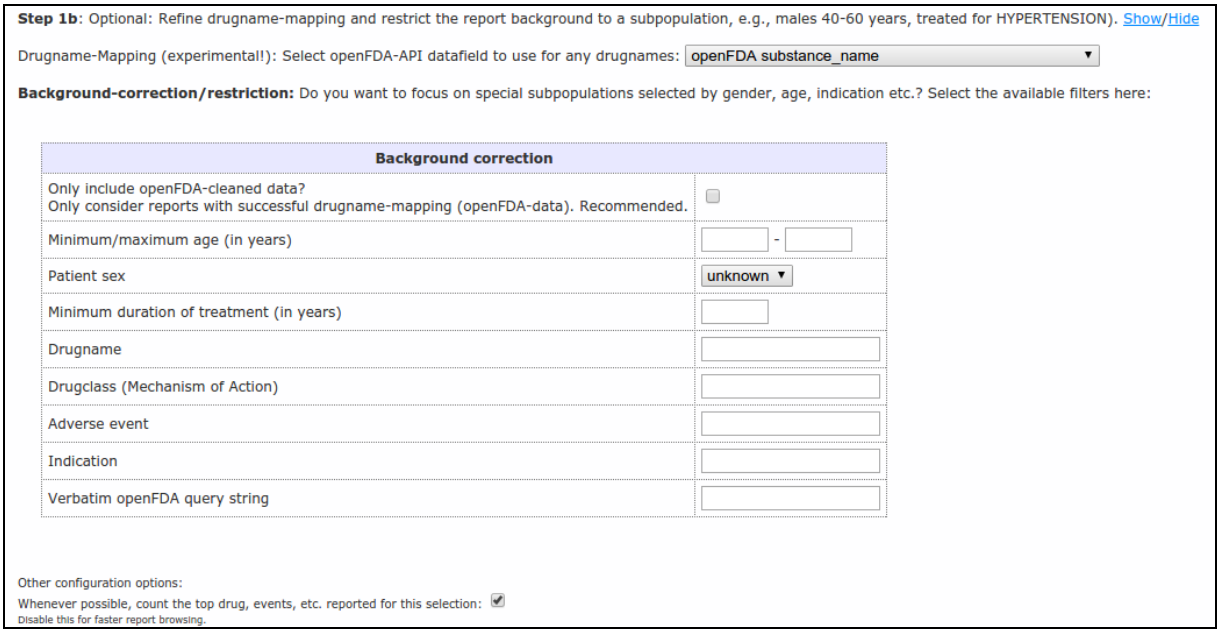
openFDA takes care of the data cleaning. The data cleaning is currently reported to be 86% and is probably lower because of some mismappings and duplicates (Shin 2014).
Before 2015-08-17, the fraction of reports with openFDA-enabled drugname mapping was 87%.
On 2015-08-17, the FDA updated the database and the drugname-mapping. The mapped fraction is now „just“ 81%. However, it appears that several mismappings were corrected: E.g., before 2015-08-17, the product „IBUPROFEN“ was incorrectly mapped to the active substances „DIPHENHYDRAMINE CITRATE + IBUPROFEN“.

4.Screenshots

OpenVigilFDA offers data extraction, counting and analysis interfaces similar to those of OpenVigil 1 or 2. Furthermore, clinical and scientific scenarious are available:



You can define a certain population background to focus on a certain subpopulation or to exclude confounding factors:



Your subpopulation of interest is further analysed and the drugs, events and indications being frequently found in these reports are shown. They might indicate any confounders. E.g., the antiemetic ondansetron appears to be associated with severe disorders of the blood. Looking at the top co-prescribed drugs, it is easy to see that this finding is confounded by the frequent use of (emetic!) chemotherapeutics like cisplatin together with ondansetron.

Open Vigil FDA safety report browser for selection drug (MEROPENEM) and/or event ()

No background correction used.
Constructed openFDA API query: https://api.fda.gov/drug/event.json?search=(patient.drug.openfda.substance_name:%22MEROPENEM%22)

Copy table below to clipboard

Last database update	2015-08-17
Number of **matching records for this selection/group**	**3979**
Possible Confounders: Which drugs, events, indications, ages or sex are most frequent among the subpopulation selected above? **Use them to refine the subpopulations you want to compare (e.g., unmasking signals by using (NOT this drug)) or include them into the background correction**	
Gender distribution	2122 (53.33%) male 1612 (40.51%) female 100 (2.51%) unknown
Age distribution Age (Number of reports)	70 (84) 63 (66) 60 (66) 67 (2) More results Show/Hide
Top drugs Generic Name (Number of reports)	MEROPENEM (3979) VANCOMYCIN HYDROCHLORIDE (1116) FUROSEMIDE (611) FLUCONAZOLE (584) More results Show/Hide
Top medicinalproducts Productname (Number of reports)	MEROPENEM (3979) VANCOMYCIN (984) FLUCONAZOLE (500) FUROSEMIDE (425) More results Show/Hide
Top drugclasses MoA Mechanism of Action (Number of reports)	Corticosteroid Hormone Receptor Agonists [MoA] (1025) Cytochrome P450 3A4 Inhibitors [MoA] (1010) Cytochrome P450 2C19 Inhibitors [MoA] (653) Cytochrome P450 2C9 Inhibitors [MoA] (614) More results Show/Hide
Top adverse events Event (Number of reports)	PYREXIA (272) SEPSIS (199) PNEUMONIA (185) RESPIRATORY FAILURE (163) More results Show/Hide
Top indications Indication (Number of reports)	PRODUCT USED FOR UNKNOWN INDICATION (546) PROPHYLAXIS (361) PNEUMONIA (267) SEPSIS (222) More results Show/Hide

Selections can be counted. Below is an example of the age distribution of all patients having issues with meropenem:

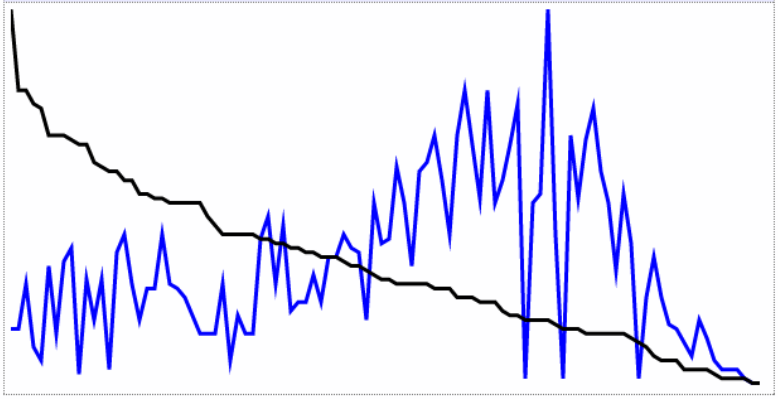
Open Vigil FDA list of counts for selection drug (MEROPENEM) and/or event ()

No background correction used.
Constructed openFDA API query: https://api.fda.gov/drug/event.json?search=(patient.drug.openfda.substance_name:%22MEROPENEM%22)&count=patient.patientonsetage

Copy table below to clipboard

Last database update	2015-08-17
Number of **term:count** pairs for factor patient.patientonsetage	**100**

Histogram
click to draw frequency of counts ordered by count (black)
click to draw frequency of counts ordered by term or date (blue)



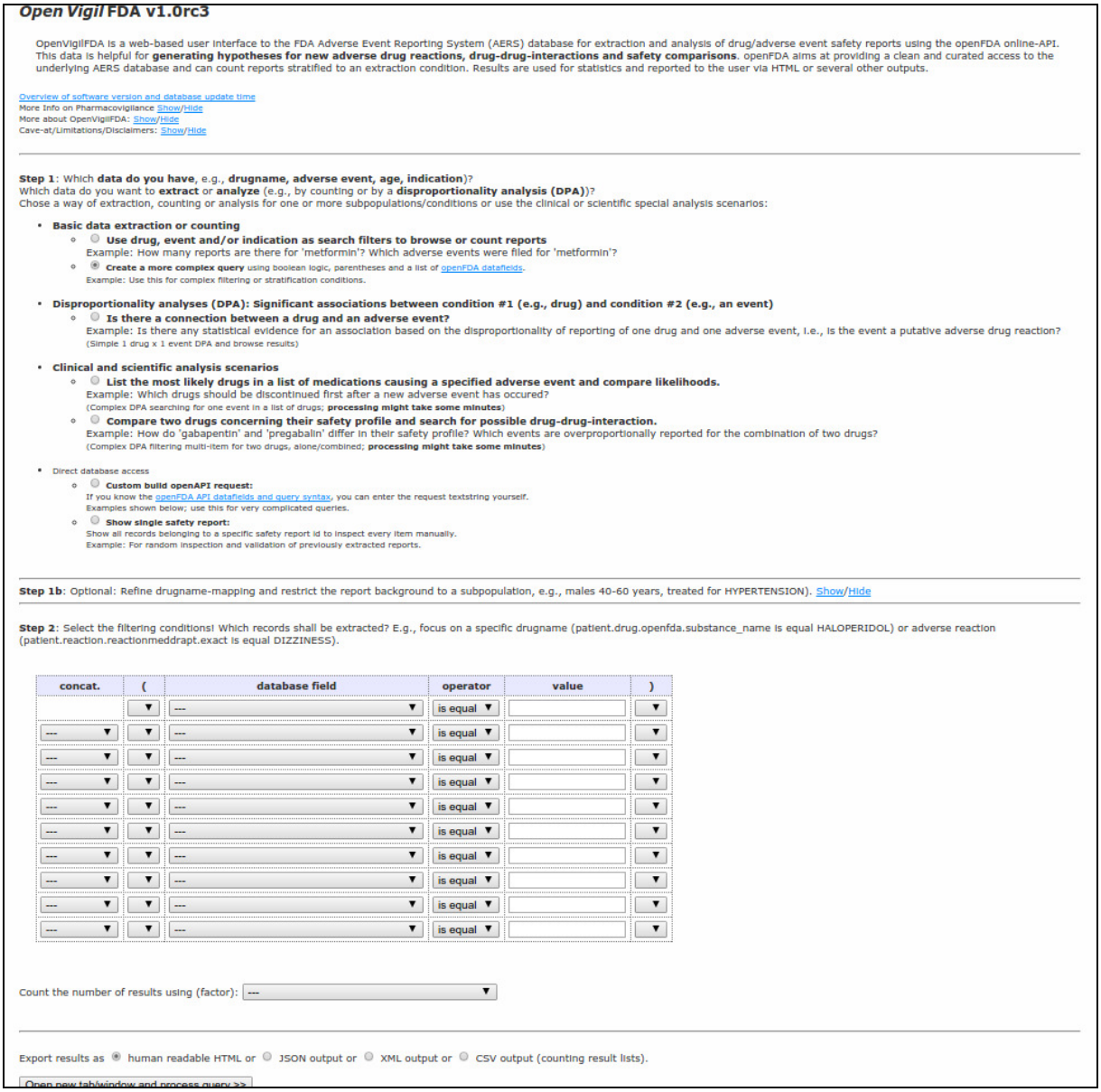
Counting results Show/Hide

Copy table below to clipboard

patient.patientonsetage	count
70	84
63	66
60	66
67	2
75	62
72	56

openFDA reports back the top-100-items for each count. The black line is an histogram of the original openFDA data, the blue line is an histogram with sorted keys (i.e., age sorted numeric).

Complex queries can be constructed with either a GUI:



Open Vigil FDA v1.0rc3

OpenVigilFDA is a web-based user interface to the FDA Adverse Event Reporting System (AERS) database for extraction and analysis of drug/adverse event safety reports using the openFDA online-API. This data is helpful for **generating hypotheses for new adverse drug reactions, drug-drug-interactions and safety comparisons**. openFDA aims at providing a clean and curated access to the underlying AERS database and can count reports stratified to an extraction condition. Results are used for statistics and reported to the user via HTML or several other outputs.

Overview of software version and database update time
More Info on Pharmacovigilance Show/Hide
More about OpenVigilFDA: Show/Hide
Cave-at/Limitations/Disclaimers: Show/Hide

Step 1: Which **data do you have**, e.g., **drugname, adverse event, age, indication**)?
Which data do you want to **extract** or **analyze** (e.g., by counting or by a **disproportionality analysis (DPA)**)?
Chose a way of extraction, counting or analysis for one or more subpopulations/conditions or use the clinical or scientific special analysis scenarios:

- **Basic data extraction or counting**
  - ○ **Use drug, event and/or indication as search filters to browse or count reports**
    Example: How many reports are there for 'metformin'? Which adverse events were filed for 'metformin'?
  - ◉ **Create a more complex query** using boolean logic, parentheses and a list of openFDA datafields.
    Example: Use this for complex filtering or stratification conditions.
- **Disproportionality analyses (DPA): Significant associations between condition #1 (e.g., drug) and condition #2 (e.g., an event)**
  - ○ **Is there a connection between a drug and an adverse event?**
    Example: Is there any statistical evidence for an association based on the disproportionality of reporting of one drug and one adverse event, i.e., is the event a putative adverse drug reaction?
    (Simple 1 drug x 1 event DPA and browse results)
- **Clinical and scientific analysis scenarios**
  - ○ **List the most likely drugs in a list of medications causing a specified adverse event and compare likelihoods.**
    Example: Which drugs should be discontinued first after a new adverse event has occured?
    (Complex DPA searching for one event in a list of drugs; **processing might take some minutes**)
  - ○ **Compare two drugs concerning their safety profile and search for possible drug-drug-interaction.**
    Example: How do 'gabapentin' and 'pregabalin' differ in their safety profile? Which events are overproportionally reported for the combination of two drugs?
    (Complex DPA filtering multi-item for two drugs, alone/combined; **processing might take some minutes**)
- Direct database access
  - ○ **Custom build openAPI request:**
    If you know the openFDA API datafields and query syntax, you can enter the request textstring yourself.
    Examples shown below; use this for very complicated queries.
  - ○ **Show single safety report:**
    Show all records belonging to a specific safety report id to inspect every item manually.
    Example: For random inspection and validation of previously extracted reports.

Step 1b: Optional: Refine drugname-mapping and restrict the report background to a subpopulation, e.g., males 40-60 years, treated for HYPERTENSION). Show/Hide

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Step 2: Select the filtering conditions! Which records shall be extracted? E.g., focus on a specific drugname (patient.drug.openfda.substance_name is equal HALOPERIDOL) or adverse reaction (patient.reaction.reactionmeddrapt.exact is equal DIZZINESS).

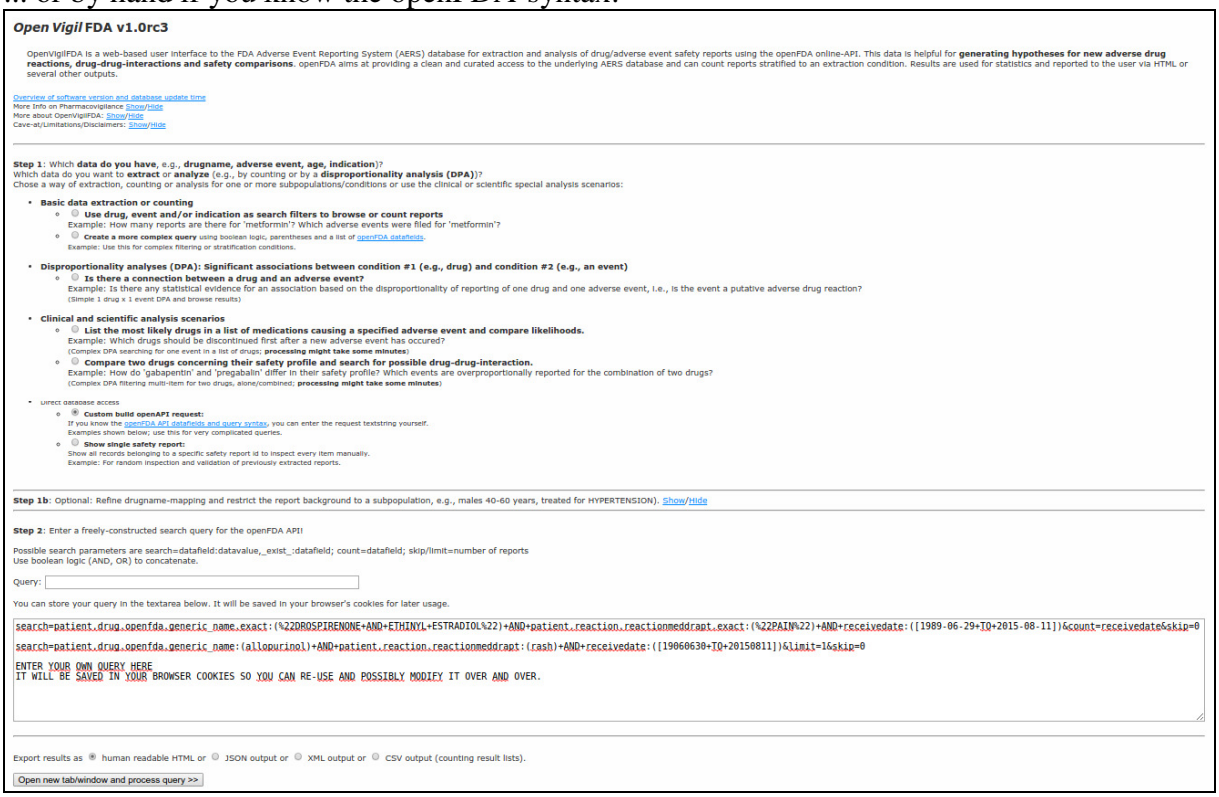
concat.	(	database field	operator	value	)
		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		
---		---	is equal		

Count the number of results using (factor): ---

Export results as ◉ human readable HTML or ○ JSON output or ○ XML output or ○ CSV output (counting result lists).

Open new tab/window and process query >>

... or by hand if you know the openFDA-syntax:



***Open Vigil* FDA v1.0rc3**

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Step 2: Enter a freely-constructed search query for the openFDA API!

Possible search parameters are search=datafield:datavalue,_exist_:datafield; count=datafield; skip/limit=number of reports
Use boolean logic (AND, OR) to concatenate.

Query:

You can store your query in the textarea below. It will be saved in your browser's cookies for later usage.

```
search=patient.drug.openfda.generic_name.exact:(%22ROSPIRENONE+AND+ETHINYL+ESTRADIOL%22)+AND+patient.reaction.reactionmeddrapt.exact:(%22PAIN%22)+AND+receivedate:([1989-06-29+TO+2015-08-11])&count=receivedate&skip=0

search=patient.drug.openfda.generic_name:(allopurinol)+AND+patient.reaction.reactionmeddrapt:(rash)+AND+receivedate:([19060630+TO+20150811])&limit=1&skip=0

ENTER YOUR OWN QUERY HERE
IT WILL BE SAVED IN YOUR BROWSER COOKIES SO YOU CAN RE-USE AND POSSIBLY MODIFY IT OVER AND OVER.
```

Export results as human readable HTML or JSON output or XML output or CSV output (counting result lists).

Open new tab/window and process query >>

This is an example report of an analysis of disproportionality for the simple 2x2 design:
Is the use of the drug „sirolimus“ connected to the adverse event „urticaria“?

Open Vigil FDA analysis of disproportionality

No background correction used.
Extracting data (this can take up to 10 seconds)...Show/Hide

Copy table below to clipboard

Groups	This drug (SIROLIMUS)	Other drugs	Sums
This event (URTICARIA)	9 DE	28349 dE	28358 E
Other event	5667 De	4976111 de	4959096 e
Sums	5676 D	4981778 d	4987454 N (total)

Copy table below to clipboard

Disproportionality Indicators	Value	Interpretation
%DrugEvent/Drug	0.15856	Percentage of this drug-this adverse event vs this drug-all adverse events
Chi squared Yates (chisq)	16.12163	Does the 2x2 table have a normal distribution (chi squared dist.)? Values greater than 4 correspond to p<0.05.
Relative Reporting Ratio (RRR)	0.27887	These ratios compare the observed counts to expected counts and allow to quantify the additional risk/odds of the drug and event selected above compared to the general background noise. Rougly, RRR/PRR/ROR values greater than 2 indicate that this drug-adverse event-combination is 2-fold more likely than all other combinations.
Proportional Reporting Ratio (PRR)	0.27864	
Reporting Odds Ratio (ROR)	0.27877	
Information Component (IC)	-1.84233	

Interpretation: According to the criteria by Evans 2001, which requires a report count > 3 (this combination: 9) and a PRR > 2 (here: 0.3) and a Chi-squared > 4 (here: 16.1) this drug and event are probably **unrelated**.

Query execution time is 2.72 seconds.

You can also view individuel safety reports:

Open Vigil FDA safety report browser for selected reports

No background correction used.
Constructed openFDA API query: https://api.fda.gov/drug/event.json?search=safetyreportid:10003494

Copy table below to clipboard

Last database update	2015-08-17
Number of **matching records for this selection/group**	**1**
Possible Confounders: Which drugs, events, indications, ages or sex are most frequent among the subpopulation selected above? **Use them to refine the subpopulations you want to compare (e.g., unmasking signals by using (NOT this drug)) or include them into the background correction**	
Gender distribution	1 (100%) female
Age distribution Age (Number of reports)	49 (1)
Top drugs Generic Name (Number of reports)	MEROPENEM (1) GENTAMICIN SULFATE (1) CLARITHROMYCIN (1) CEFUROXIME SODIUM (1) More results Show/Hide
Top medicinalproducts Productname (Number of reports)	ZITHROMAX (1) VIBRAMYCIN (1) TIMENTIN (1) PRIMAQUINE (1) More results Show/Hide
Top drugclasses MoA Mechanism of Action (Number of reports)	P-Glycoprotein Inhibitors [MoA] (1) Cytochrome P450 3A4 Inhibitors [MoA] (1) Cytochrome P450 3A Inhibitors [MoA] (1)
Top adverse events Event (Number of reports)	Drug hypersensitivity (1)
Top indications Indication (Number of reports)	

Copy table below to clipboard

Safety report	**#10003494**
Browse reports	**- #0/1 Next >>**
Receivedate	20140312
Reporter/Company	US-PFIZER INC-2014070054
Patient age	49 years
Patient sex	female

This report lists 11 drugs.

Copy table below to clipboard

Medicinalproduct	Substance_name(s)	Drug class	Form	Dosage
ZITHROMAX	AZITHROMYCIN DIHYDRATE			500 MG, UNK
VIBRAMYCIN			CAPSULE, HARD	100 MG, UNK
CEFUROXIME	CEFUROXIME SODIUM + CEFUROXIME			UNK
GENTAMICIN SULFATE	GENTAMICIN SULFATE + GENTAMICIN			UNK

To provide detailed information about the software and dataset used for an analysis, you should include the overview page in your publication:

OpenVigilFDA overview

Copy table below to clipboard

component	status, e.g., version, release date, count
OpenVigilFDA version string:	*Open **Vigil** FDA v1.0rc3*
OpenVigilFDA license/contact/website:	GNU Public License (GPL) version 2 Project developer: ruwen.boehm@pharmakologie.uni-kiel.de Website: openvigil.sf.net
PHP version:	5.2.17
openFDA meta.disclaimer:	openFDA is a beta research project and not for clinical use. While we make every effort to ensure that data is accurate, you should assume all results are unvalidated.
openFDA meta.license:	http://open.fda.gov/license
openFDA meta.last_updated:	2015-08-17
openFDA meta.results.total for whole dataset:	4987454
openFDA meta.results.total with patient.drugs.openfda:	4084399
Percentage of openFDA-tagged safety reports:	81.89

Below is the original openFDA JSON output for further the whole resultsset for further inspection. Click on Show to enlarge the sections.

Show/Hide