



MedDRA and Pharmacovigilance in the EEA


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MedDRA MSSO Users Group Meeting
Philadelphia, 22 June 2006




New Community Legislation: Pre-Authorisation Phase

- 
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2005
 - Refers to the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use




New Community Legislation: Pre-Authorisation Phase

- 
- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) ENTR CT 4 Revision 1 April 2004
 - Detailed guidance on the European clinical trials database (EUDRACT Database) ENTR CT 5 April 2003 as amended
 - Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ENTR CT 3 Revision 2 April 2006




New Community Legislation: Pre-Authorisation Phase

- 
- Use of MedDRA for reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs):
 - The current version of MedDRA or the previous one should be used for the coding of adverse reaction terms
 - Lowest Level Terms should be used
 - Where medically appropriate, signs and symptoms can be lumped into diagnoses
 - MedDRA integrated in EudraCT database




New Community Legislation: Post-Authorisation Phase

- 
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 as amended
 - Addresses the Community code relating to medicinal products for human use
 - Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004
 - Lays down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency




New Community Legislation: Post-Authorisation Phase

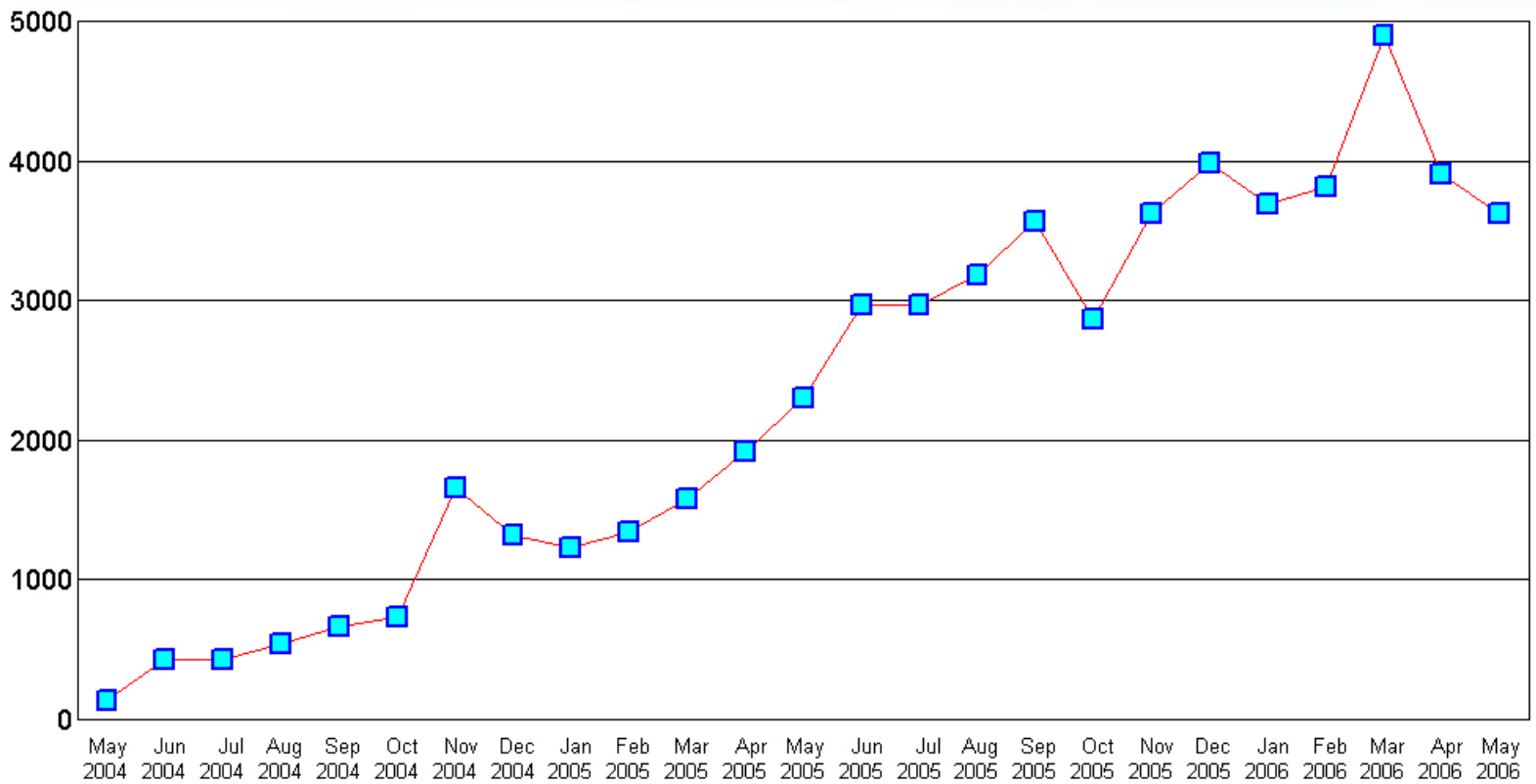
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- Volume 9A of the Rules Governing Medicinal Products in the European Union and Guidelines on Pharmacovigilance for Medicinal Products for Human Use
 - The collection, verification and presentation of adverse reaction reports to facilitate the exchange of information about human pharmacovigilance within the Community
 - Technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed format
 - The use of an internationally agreed medical terminology (MedDRA)



E-Reporting Requirements in the Pre-Authorisation Phase

- 
- Applicable to sponsors for all interventional clinical trials as of May 2004
 - All Suspected Unexpected Serious Adverse Reactions (SUSARs) are reportable electronically
 - Sponsors to report to
 - Concerned Member State(s)
 - Concerned Ethics Committees
 - EudraVigilance Clinical Trial Module (EVCTM) at the EMEA

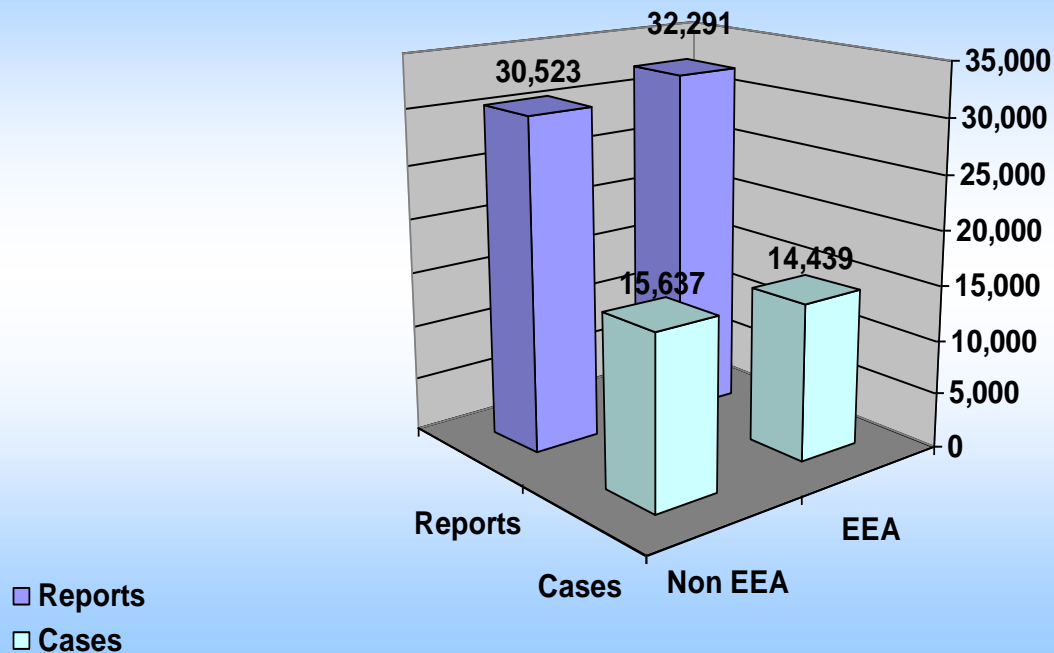
Current Implementation Status



Current Implementation Status




Number of SUSAR Reports and Cases reported by Sponsors to EVCTM: 01/05/04 - 31/05/06

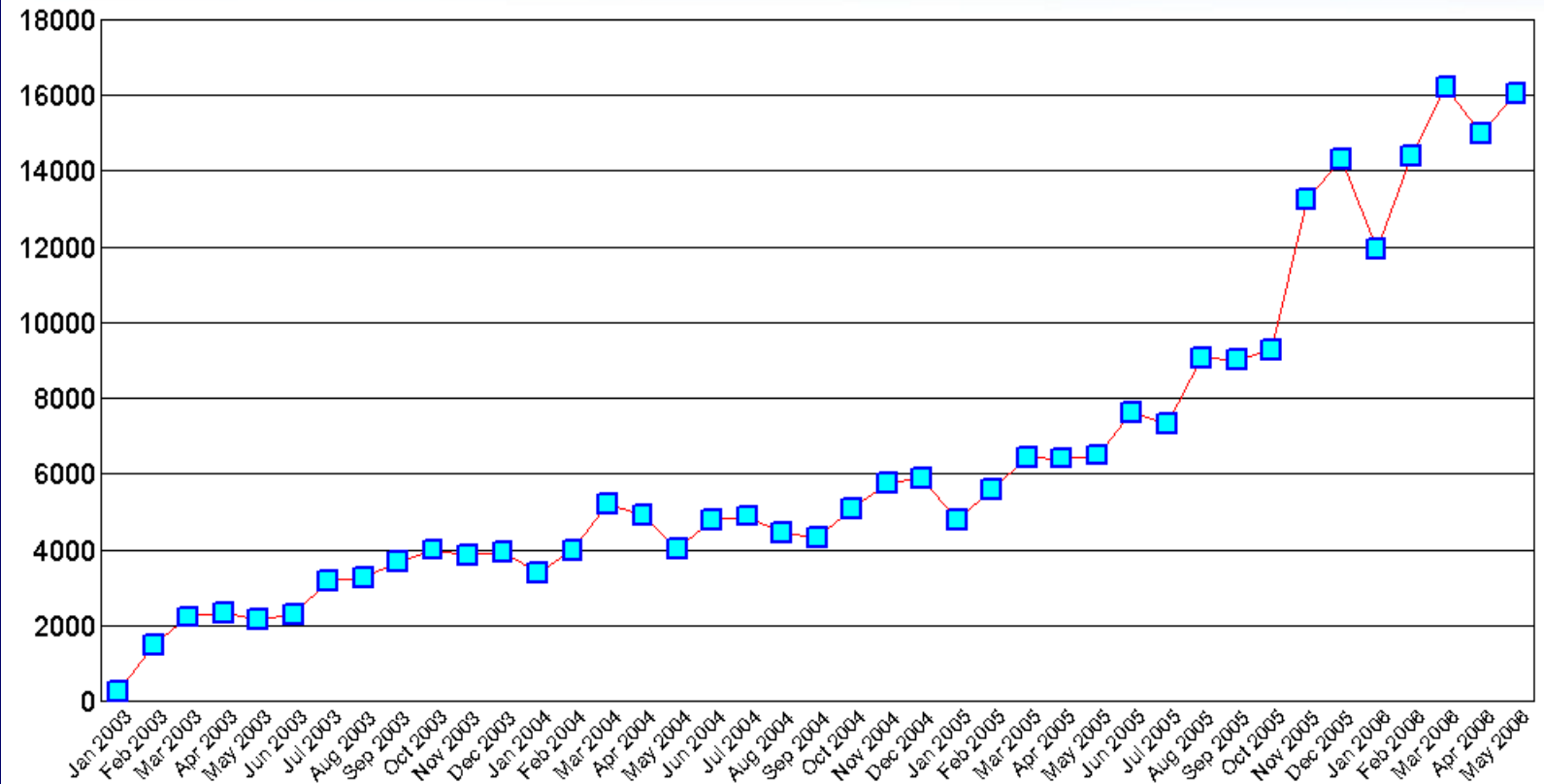




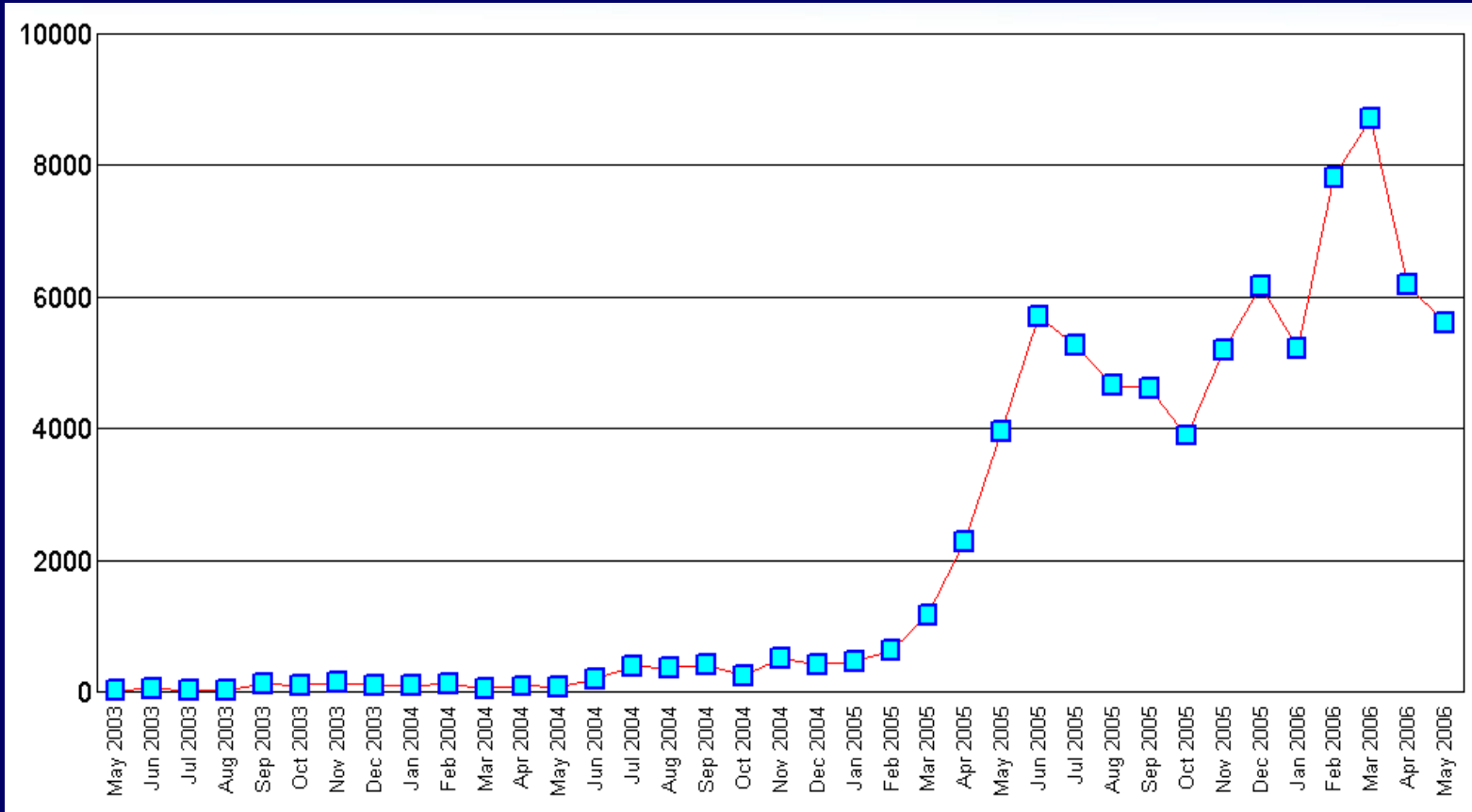
E-Reporting Requirements in the Post-Authorisation Phase

- 
- Mandatory e-reporting of ICSRs
 - As of 20 November 2005 for all medicinal products authorised in the EEA, independent of the authorisation procedure
 - Definition of exceptional circumstances that prevent electronic reporting
 - Mechanical, program, electronic or communication failure
 - Fall-back procedures to maintain expedited reporting compliance are established

Current Implementation Status



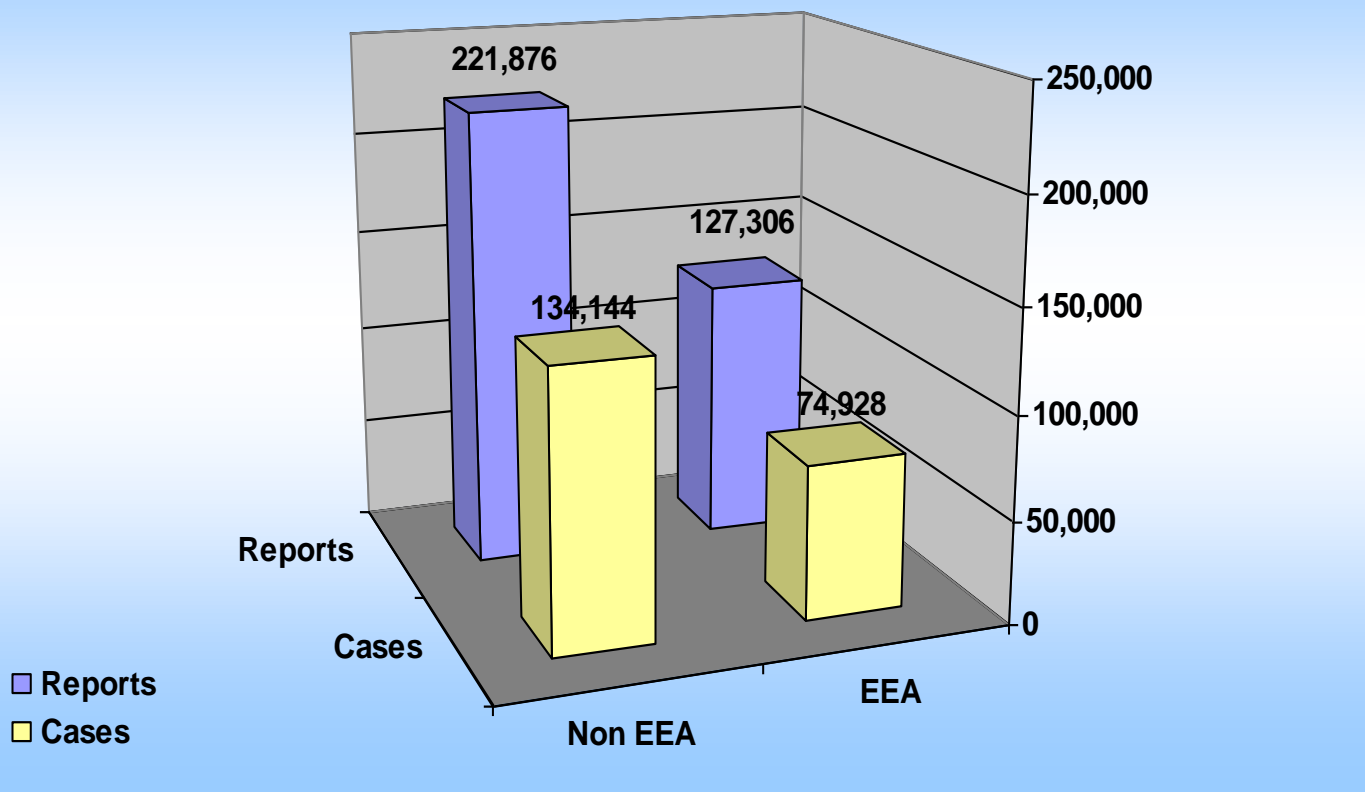
Current Implementation Status



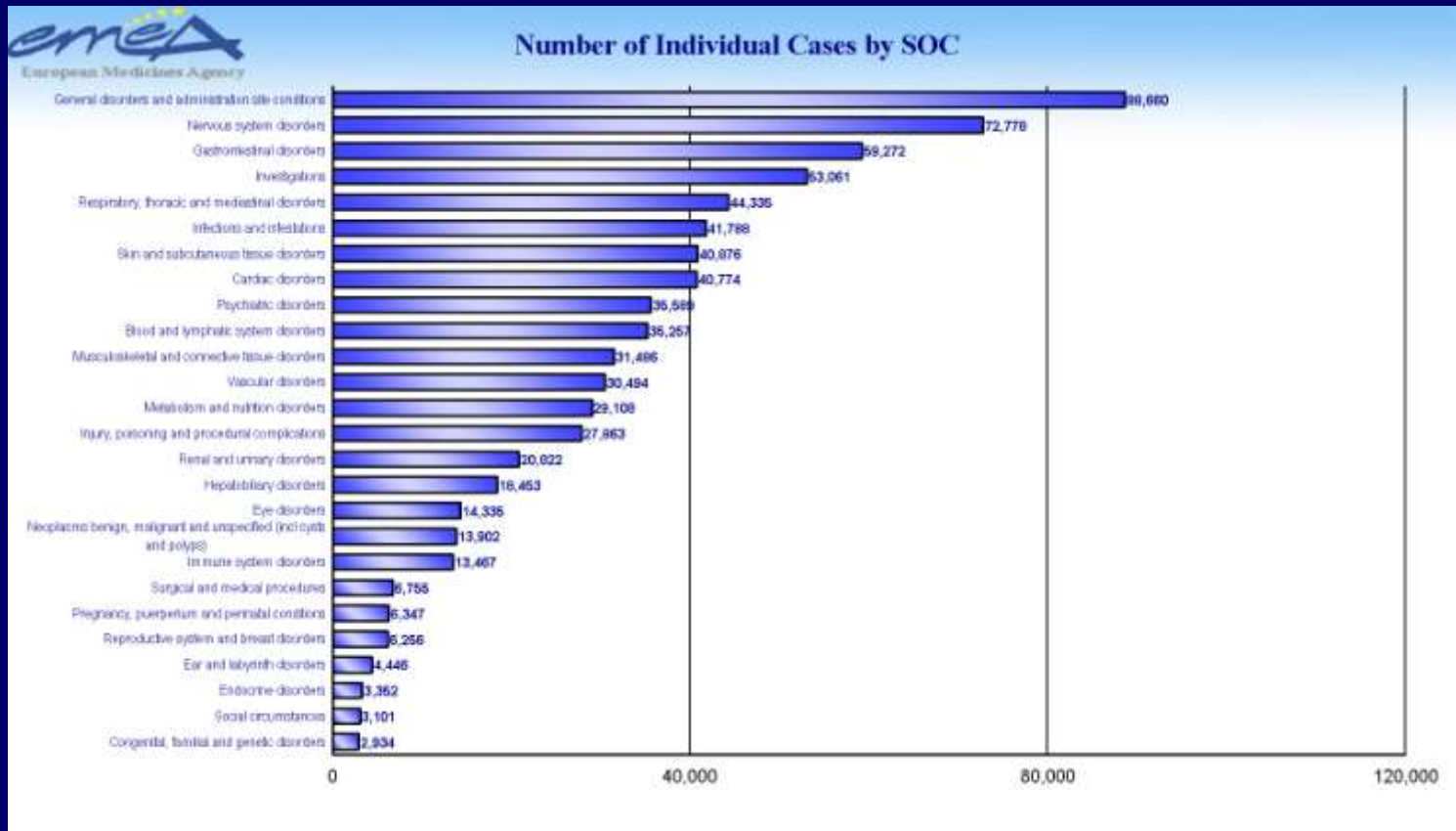
Current Implementation Status



Number of ICH ICSRs and Cases reported by MAHs and NCAs to EVPM 1/12/01-31/05/06



Current Implementation Status





New Developments



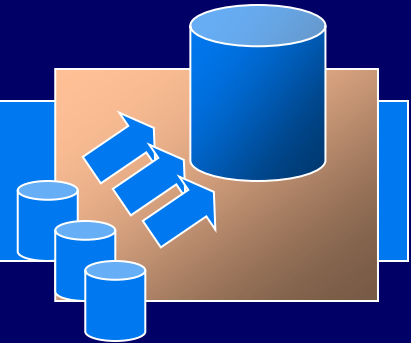
• Release of the EudraVigilance Data Analysis System

- New tool to support statistical signal detection and data analysis in the EEA
- Draft Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System currently under discussion within EMEA Scientific Committees
- National Competent Authorities, EMEA and European Commission have access to all data available
- New Community legislation will allow for ‘appropriate*’ levels of access to:
 - Marketing Authorisation Holders
 - Health Care Professionals
 - Public

* Ensuring personal data protection



EudraVigilance Data Warehouse



A Database to:



Support case review and data analysis in pharmacovigilance



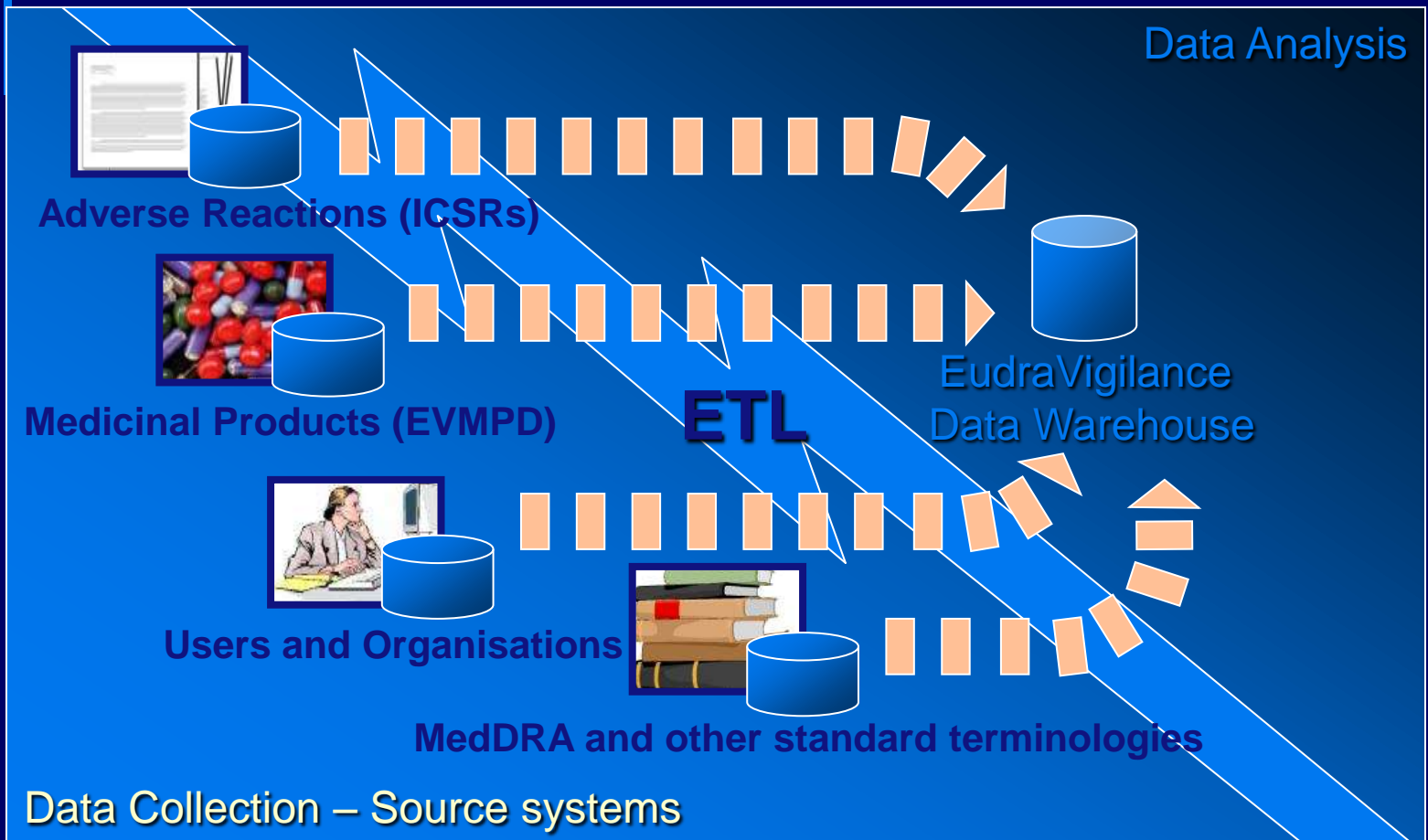
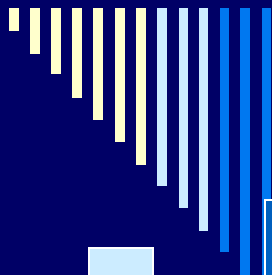
Integrate data from all EudraVigilance source systems and MedDRA terminology



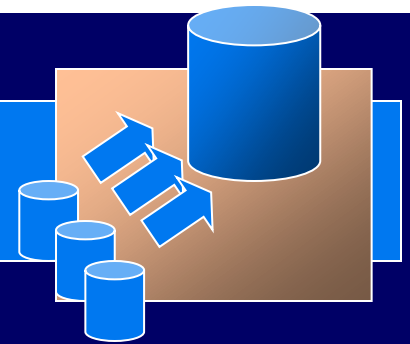
Consolidate and clean data ('data normalisation')



Preserve historical data for data analysis



EudraVigilance Data Warehouse



The ETL Process



Extract data from the EudraVigilance source systems



Transform, clean, normalise and consolidate the data



Transform: i.e. transform data to simplify queries (transform birth dates to age)



Clean: i.e. recoding medicinal product information as reported in ICSRs



Normalise: i.e. normalise measurements and measurement units

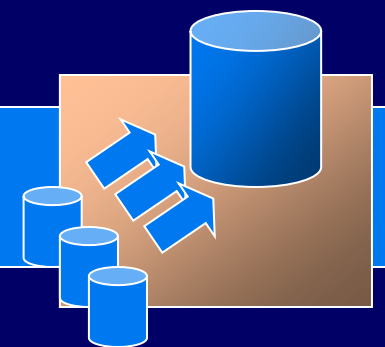


Consolidate: i.e. define time ranges as applicable for the data

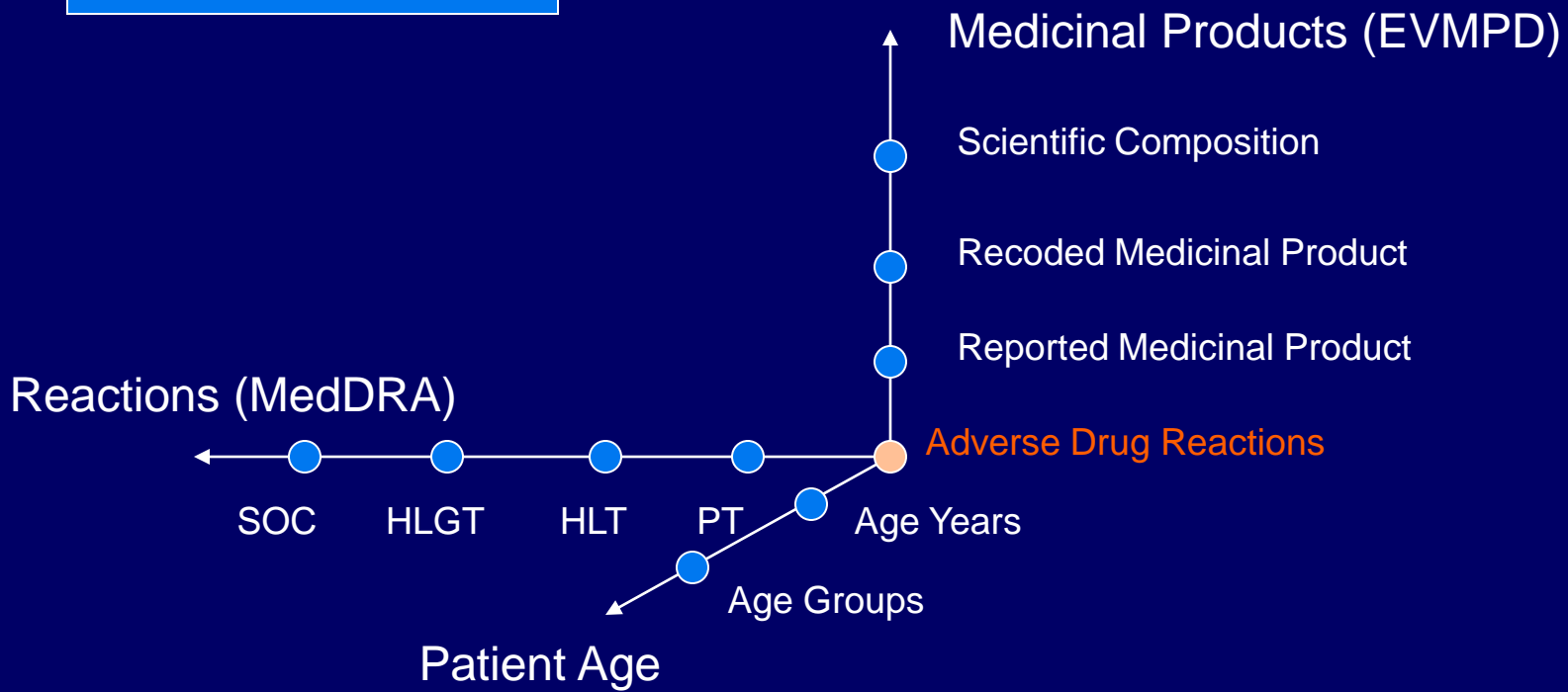


Load and populate the data in the Data Warehouse

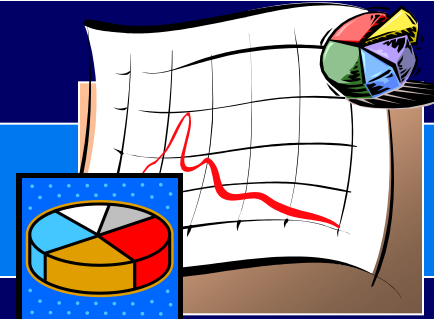
EudraVigilance Data Warehouse



Facts and Dimensions



The EudraVigilance Analysis System



User Interface for Data Analysis and Use of Statistical Signal Detection Methods in Pharmacovigilance



Standard Query Library to perform data analysis and statistical queries



Exploratory Data Analysis including options to perform queries on previous query results



Obtain information on the query (e.g. restrictions applied)

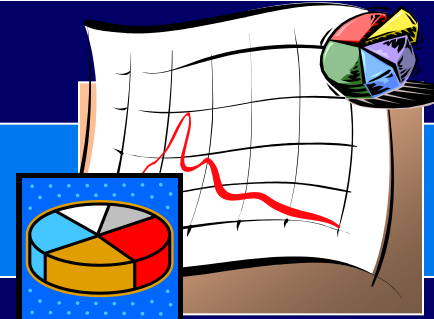


Format data grids and graphs and pivot results



Data export functionalities

The EudraVigilance Analysis System



Internet application accessible to all the 'EudraVigilance Users' after appropriate training



National Competent Authorities, EMEA and European Commission have access to all data available



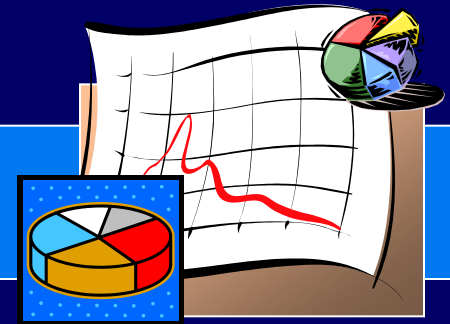
New Community legislation will allow for 'appropriate*' levels of access to:

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- Public

* Ensuring personal data protection



The EudraVigilance Analysis System

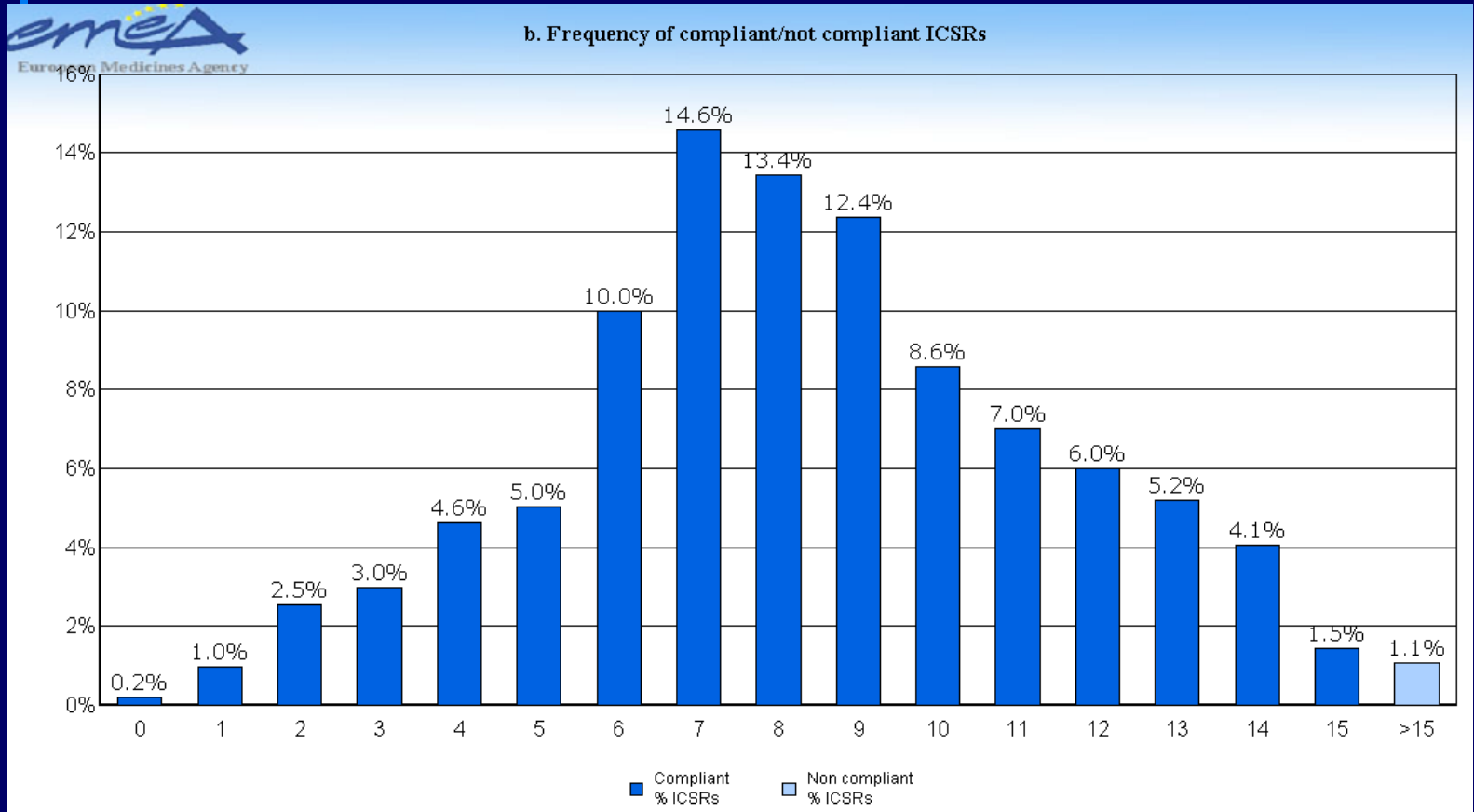


The EudraVigilance Standard Query Library

Some examples...

Administrative Queries – 15 day expedited reporting compliance

Marketing Authorisation Holders – Post Authorisation Module (01 May 06– 31 May 06)



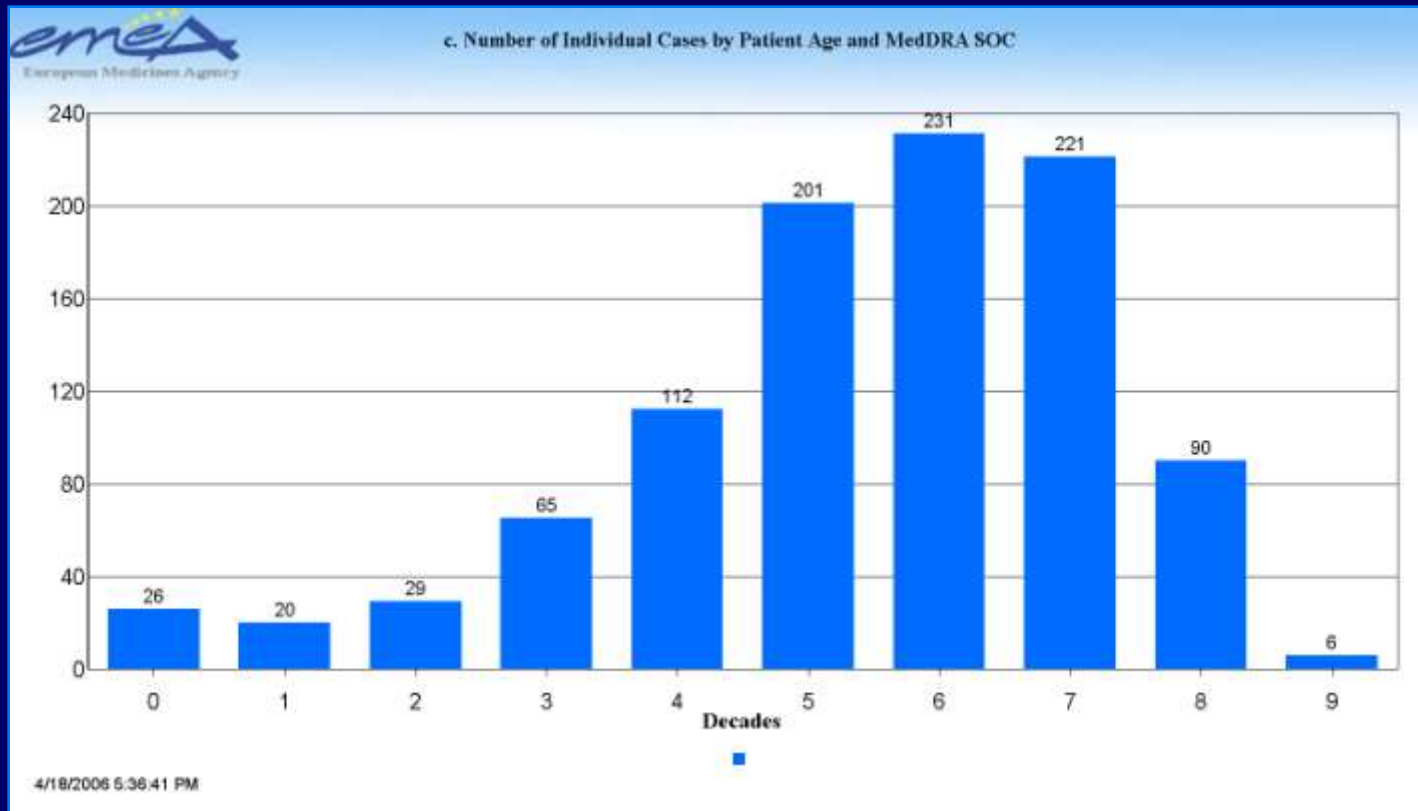
Pharmacovigilance Queries – Medicinal Product/Adverse Reaction Report

Paracetamol – Standardised MedDRA Query

Scientific Composition Group Metrics	PARACETAMOL
	Count Cases
SMQ Level 1	
Not in SMQ	6,051
Rhabdomyolysis/Myopathy (SMQ) (Broad)	613
Liver related investigations, signs and symptoms (SMQ) (Broad)	439
Torsade de Pointes/QT prolongation (SMQ) (Broad)	320
Acute renal failure (SMQ) (Broad)	319
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) (Broad)	272
Acute renal failure (SMQ) (Narrow)	209
Severe cutaneous adverse reactions (SMQ) (Broad)	183
Cholestasis and jaundice of hepatic origin (SMQ) (Broad)	145
Hepatitis, non-infectious (SMQ) (Broad)	141
Severe cutaneous adverse reactions (SMQ) (Narrow)	112
Rhabdomyolysis/Myopathy (SMQ) (Narrow)	57
Torsade de Pointes/QT prolongation (SMQ) (Narrow)	52
Haemolytic disorders (SMQ) (Broad)	46
Haemolytic disorders (SMQ) (Narrow)	46
Possible liver-related coagulation and bleeding disturbances (SMQ) (Broad)	42
Liver infections (SMQ) (Broad)	12
Liver neoplasms, benign (SMQ) (Broad)	8
Liver neoplasms, malignant and unspecified (SMQ) (Broad)	3
Congenital, familial, neonatal and genetic disorders of the liver (SMQ) (Broad)	2

Administrative Queries – Number of Cases by Age and MedDRA SOC

Paracetamol – Reaction MedDRA SOC = Cardiac Disorders



The EudraVigilance Standard Query Template

2. Select an output level from the following MedDRA hierarchy * (Required)

The system will report on the selected output level of the MedDRA hierarchy. The default choice is the Preferred Term. This prompt allows only one selection.

- SMQ Level 1
- Reaction SOC
- Reaction HLT
- Reaction HLT
- Reaction PT Multiaxial
- Reaction PT

2. Select an output level from the Medicinal Product hierarchy * (Required)

The system will report on the selected output level from the Medicinal Product hierarchy. The default choice is the Scientific Composition Group. This prompt allows only one selection.

- Scientific Composition Group
- Scientific Composition
- Recoded Medicinal Product
- Reported Medicinal Product

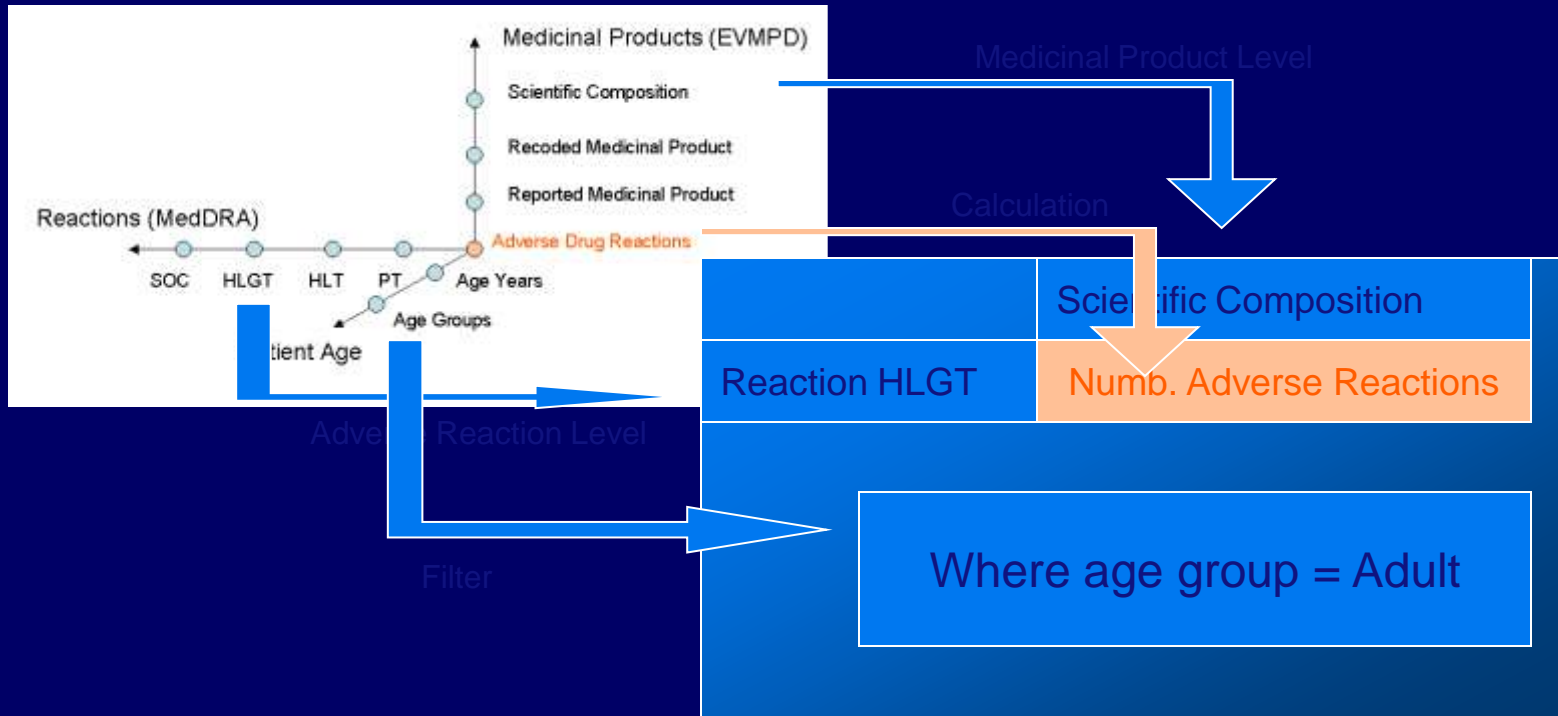
The EudraVigilance Standard Query Template

5. Select any other additional criteria to filter the report results

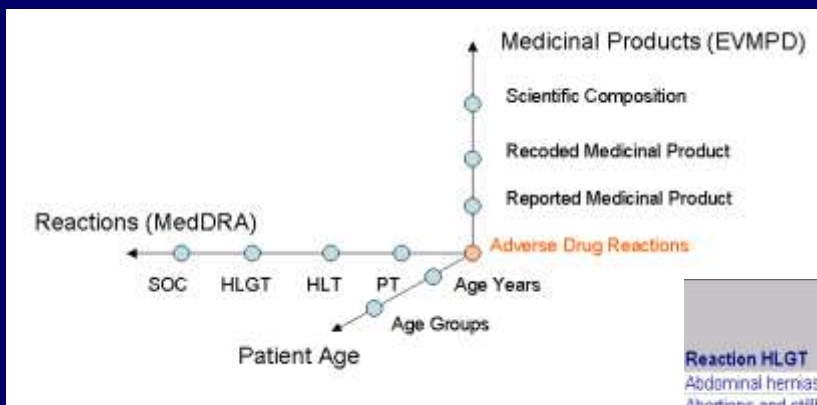
No answer is required for this prompt.

- 1 Report Type (E2B Field - A.1.4)
- 2 EudraVigilance Document Type
- 3 Receive Date (E2B Field - A.1.6.b)
- 4 EudraVigilance Message Gateway Date
- 5 Characterisation of Medicinal Product role (E2B Field - B.4.k.1)
- 6 Term Highlighted (E2B Field - B.4.k.1)
- 7 Primary Source countries (E2B Field - A.1.2)
- 8 Primary Source Country EEA/NON EEA (Hierarchy on Primary Source Country E2B Field - A.1.2)
- 9 Organisations sending the ICSRs (E2B Field - M.1.5)
- 10 Patient Sex (E2B Field - B.1.5)
- 11 Age range (E2B Field - B.1.2.2b)
- 12 Age group (E2B Field - B.1.2.3)
- 13 Medicinal Product Batch Number - select particular drug from the list (E2B Field - B.4.k.3)
- 14 Medicinal Product Batch Number - search for particular text of drug batch number (E2B Field - B.4.k.3)
- 15 Seriousness criteria (E2B fields - B.1.5.2)
- 16 Sponsor study number (E2B Field - A.2.3.2)
- 17 Only Master Report - Duplicated Detection (No History Management)
- 18 Reaction Outcome (E2B fields - B.2.i.8)

EudraVigilance Standard Query Template



EudraVigilance Standard Query Template



Reaction HLTG	Scientific Composition Metrics	PARACETAMOL
		Count Cases
Abdominal hernias and other abdominal wall conditions		40
Abortions and stillbirth		21
Acid-base disorders		71
Adjustment disorders (incl subtypes)		4
Administration site reactions		72
Adrenal gland disorders		5
Age related factors		1
Allergic conditions		183
Anaemias nonhaemolytic and marrow depression		370
Anal and rectal conditions NEC		13
Aneurysms and artery dissections		29
Angioedema and urticaria		105
Anterior eye structural change, deposit and degeneration		29
Anxiety disorders and symptoms		250
Appetite and general nutritional disorders		169
Arteriosclerosis, stenosis, vascular insufficiency and necrosis		76

Signal Detection based on Statistical Methods



Implementation of calculations to support statistical signal detection: Approach to prioritise case review



Proportional Reporting Ratio (PRR)




95% PRR Confidence Interval



χ^2 (Chi Square Test)

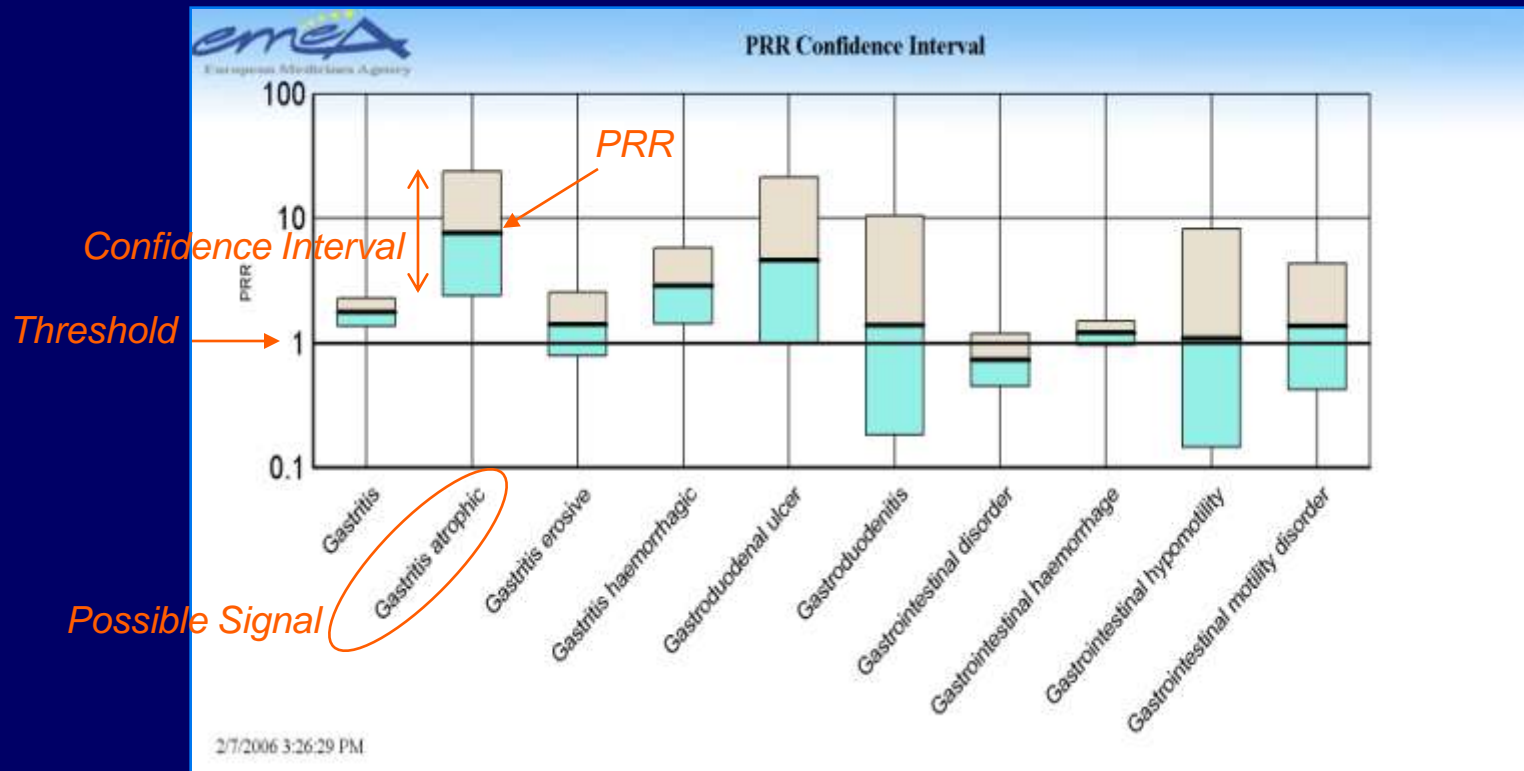


All **potential statistical signals are medically evaluated** based on the complete case information including case narratives



Draft Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System currently under discussion within EMEA Scientific Committees

Signal Detection based on Statistical Methods



Exploratory Data Analysis

PRR Monitor

Reaction SOC: Gastrointestinal disorders		Scientific Composition Group: PARACETAMOL				
		Metrics	PRR (SOC)	PRR (HLGT)	PRR (HLT)	PRR (PT)
Reaction HLGT	Reaction HLT	Reaction PT				
Gastrointestinal inflammatory conditions						
Colitis (excl infective)						
		Colitis	1.39	1.61	1.07	0.75
		Colitis collagenous	1.39	1.61	1.07	2.03
		Colitis ischaemic	1.39	1.61	1.07	1.50
		Colitis microscopic	1.39	1.61	1.07	16.20
		Colitis ulcerative	1.39	1.61	1.07	0.69
		Enterocolitis haemorrhagic	1.39	1.61	1.07	0.80
		Neutropenic colitis	1.39	1.61	1.07	6.08
		Maximum	1.39	1.61	1.07	16.20
Gastritis (excl infective)						
		Gastritis	1.39	1.61	2.54	2.29
		Gastritis atrophic	1.39	1.61	2.54	13.89
		Gastritis haemorrhagic	1.39	1.61	2.54	3.91
		Gastroduodenitis	1.39	1.61	2.54	1.74
		Reflux gastritis	1.39	1.61	2.54	8.10
		Maximum	1.39	1.61	2.54	13.89
Gastrointestinal inflammatory disorders NEC						
		Crohn's disease	1.39	1.61	1.14	1.67
		Duodenitis	1.39	1.61	1.14	2.26
		Enteritis	1.39	1.61	1.14	0.84
		Ileitis	1.39	1.61	1.14	1.74
		Inflammatory bowel disease	1.39	1.61	1.14	0.22
		Maximum	1.39	1.61	1.14	2.26

Possible Signal

Exploratory Data Analysis Drill to “Line Listing”

Safety Report	Case Report Num.	Report Type	Document Type	Receive Date	Receipt Date	Gateway Date	Age	Birthdate	Sex	Serious	Serious. Death	Serious. Disabling	Serious. Hosp.	Serious. Life Threat.	Serious. Other	CIO
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	08 Mar 2004	71	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	08 Mar 2004	70	Not Specified	Female	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	08 Mar 2004	52	Not Specified	Female	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	65	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	66	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	60	Not Specified	Female	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	46	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	72	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	66	Not Specified	Male	Yes	No	No	No	No	Yes	
		Report from Studies	PM ICSR	24 Feb 2004	24 Feb 2004	09 Mar 2004	84	Not Specified	Female	Yes	No	No	No	No	Yes	

CIOMS


Exploratory Data Analysis Drill to “CIOMS”

Suspect Adverse Reaction Report						US- [REDACTED]	
(Page 1 of 2)							
I. REACTION INFORMATION							
1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE 71 Year	3. SEX	4. WEIGHT	5. HEIGHT	6. EVENT ONSET
<p>7+13. DESCRIBE REACTION(S) (including relevant lab data)</p> <p>Verbatim Term: Macular edema Reaction / Event (MedDRA 11t): Macular edema Outcome of Reaction: Verbatim Term: Peripheral edema Reaction / Event (MedDRA 11t): Peripheral edema Outcome of Reaction: Verbatim Term: Condition aggravated Reaction / Event (MedDRA 11t): Condition aggravated Outcome of Reaction: Verbatim Term: Visual acuity decreased Reaction / Event (MedDRA 11t): Visual acuity decreased Outcome of Reaction:</p> <p>Case Narrative: This case was reported in the literature and described the occurrence of macular edema in a 71 year old male subject who received [REDACTED] and was included in a retrospective chart review of diabetic patients who developed worsening of diabetic macular edema and fluid retention as a consequence of glitazone use. The patients medical history included a four year history of type II diabetes, respiratory insufficiency and hypertension. Concurrent medication included glucovance.</p> <p>In April 2002, the subject started [REDACTED] (unknown dose). Following an unknown period of exposure to [REDACTED] he subject was enrolled on the study. Prior to starting [REDACTED] 2000, the subjects vision was 20/20 (OD) 20/150 (OS). However, in May 2003, his vision became 20/100</p> <p><small>See our file at also</small></p>							<p>8. - 12. CHECK ALL APPROPRIATE TO ADVERSE REACTION</p> <p><input type="checkbox"/> PATIENT DIES AS OUTCOME OF EVENT</p> <p><input type="checkbox"/> RESULTED IN OR PROLONGED PATIENT HOSPITALISATION</p> <p><input type="checkbox"/> INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY</p> <p><input type="checkbox"/> LIFE THREATENING</p> <p><input type="checkbox"/> CONGENITAL ANOMALY</p> <p><input type="checkbox"/> CLINICALLY SIGNIFICANT/ REQUIRED INTERVENTION</p> <p><input type="checkbox"/> OTHER</p>



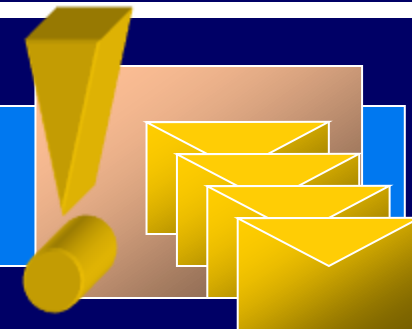
The EudraVigilance Information Delivery System



- 
- Run specific queries for medicinal products on routine basis
 - Used to deliver information directly to interested parties:
 - Rapporteurs, Co-Rapporteurs, Reference Member State
 - EMA Pharmacovigilance Sector
 - Qualified Person Responsible Person for Pharmacovigilance (QP of MAH) in next stage
 - Different 'information templates' are available

The EudraVigilance Information Delivery System

Reaction Monitoring Report



Reaction SOC: Gastrointestinal disorders Scientific Composition Group: PARACETAMOL

1

Reaction PT	Metrics	PRR (-)	PRR	PRR (+)	New	New EEA	New Non EEA	New Fatal	Total	EEA	Non EEA	Fatal
Gastric ulcer haemorrhage		2.83	4.03	5.73	31	4	20	2	31	4	20	2
Gastric ulcer perforation		1.34	2.98	6.62	6	2	1	1	6	2	1	1
Gastric varices		0.68	4.86	34.51	1	0	1	0	1	0	1	0
Gastritis		1.79	2.29	2.94	62	7	53	7	62	7	53	7
Gastritis atrophic		5.21	13.89	37.01	4	0	4	0	4	0	4	0
Gastritis erosive		1.00	1.77	3.11	12	2	10	0	12	2	10	0
Gastritis haemorrhagic		2.03	3.91	7.51	9	3	6	2	9	3	6	2
Gastroduodenal ulcer		1.74	6.94	27.77	2	2	0	0	2	2	0	0
Gastroduodenitis		0.24	1.74	12.33	1	0	1	0	1	0	1	0
Gastrointestinal disorder		0.55	0.88	1.42	17	1	16	2	17	1	16	2
Gastrointestinal haemorrhage		1.20	1.49	1.85	82	17	64	28	82	17	64	28
Gastrointestinal hypomotility		0.19	1.35	9.59	1	0	1	0	1	0	1	0
Gastrointestinal motility disorder		0.55	1.70	5.26	3	1	2	2	3	1	2	2
Gastrointestinal mucosal necrosis		1.14	8.10	57.52	1	1	0	1	1	1	0	1
Gastrointestinal necrosis		0.24	0.95	3.81	2	0	2	1	2	0	2	1
Gastrointestinal pain		0.21	0.82	3.29	2	0	2	0	2	0	2	0
Gastrointestinal perforation		0.35	1.09	3.37	3	1	2	1	3	1	2	1
Gastrointestinal tract mucosal discolouration		1.14	8.10	57.52	1	0	1	0	1	0	1	0
Gastrointestinal ulcer		0.62	1.92	5.95	3	0	3	0	3	0	3	0
Gastrointestinal ulcer haemorrhage		1.59	4.23	11.26	4	2	2	1	4	2	2	1
Gastrointestinal ulcer perforation		1.71	12.15	86.28	1	1	0	0	1	1	0	0
Gastrooesophageal reflux disease		2.51	3.10	3.83	86	4	81	4	86	4	81	4



Thank You

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