



## **FDA Safety Review Probing Drospirenone's Potential Association With VTE Risk.**

The [Wall Street Journal](#) (6/1, Dooren, Subscription Publication) reports the Food and Drug Administration announced it is conducting a safety review of oral contraceptive drugs that contain drospirenone to evaluate the risk for venous thromboembolism (VTE) associated with these products.

The [New York Times](#) /Bloomberg News (6/1, B5, Subscription Publication) reports, "Two recent reports in the British Medical Journal found a twofold to threefold greater risk of blood clots in women taking pills like Bayer's Yaz," the FDA said in a [statement](#). The agency expects to "have results later this summer of an 800,000-person study it commissioned to examine the risks."

[Medscape](#) (5/31, Hitt) noted that the FDA advised healthcare professionals to continue following the "recommendations on drug labels when prescribing oral contraceptive products that contain drospirenone." In addition, clinicians should "discuss the known benefits and potential risks of drospirenone-containing products with patients and educate them about the signs and symptoms of VTE, a term that incorporates both deep vein thrombosis and pulmonary embolism."

Additionally, [AFP](#) (5/31) reported that the European Medicines Agency "concluded on May 27 that such birth control pills carry a higher risk" of VTE and that warning labels "should be updated accordingly." However, the EMA "noted the overall risk of blood clot from any birth control method remains small and stopped short of advising women to stop taking pills containing drospirenone." [Reuters](#) (6/1)

## A Signal is:

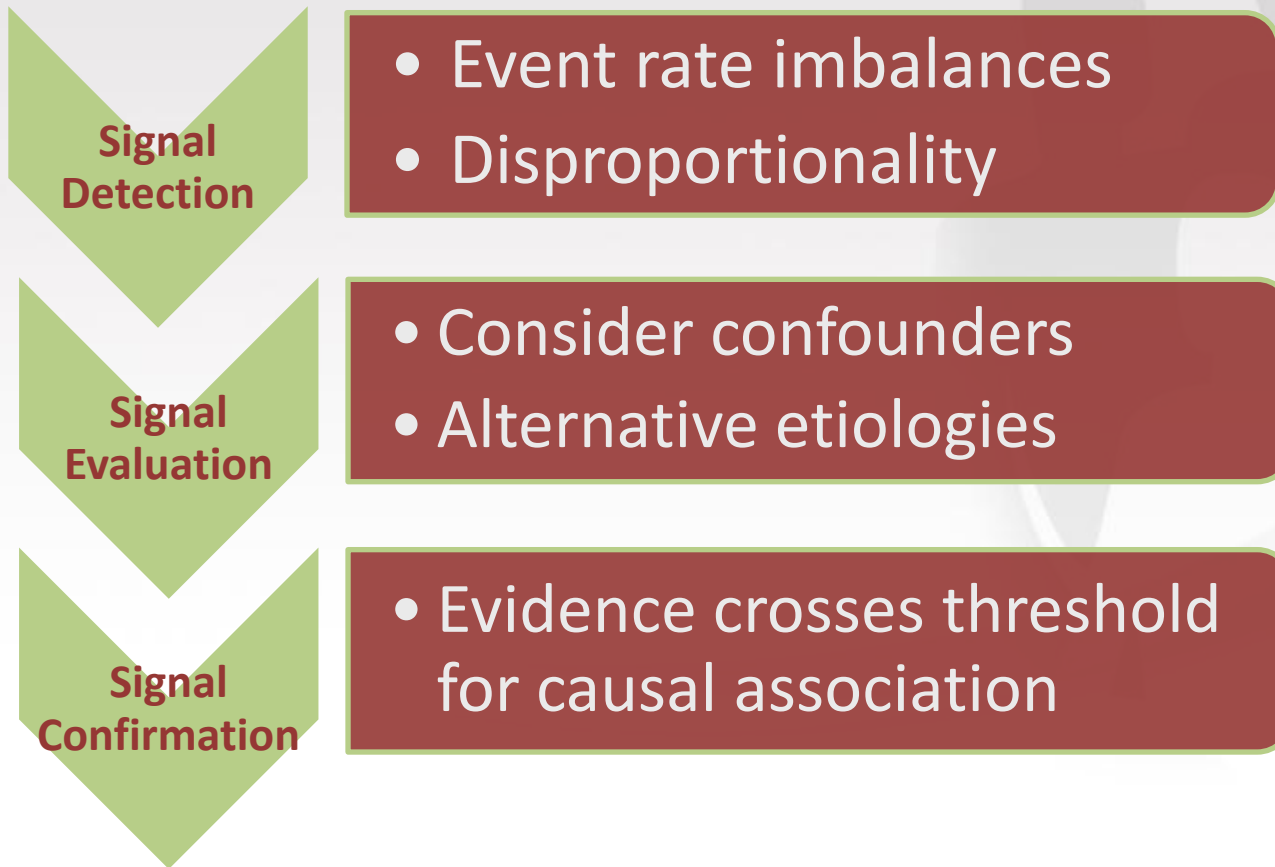
“....an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance.”\*

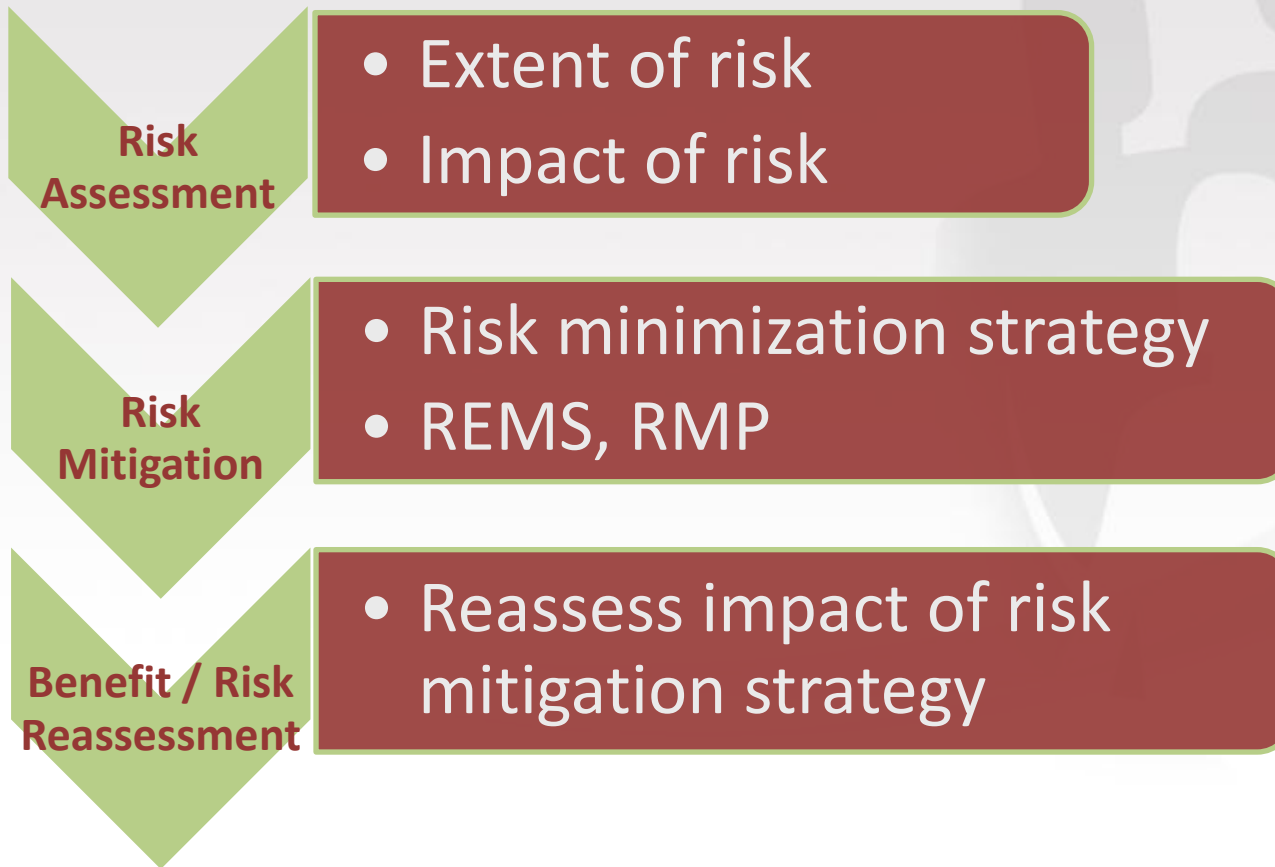
## A Signal is Not:

Information defining or confirming new causal association.

\* CIOMS Working Group VIII Report, 2010









## Easy to Identify

- Single cases of rare events
- Stevens Johnson Syndrome, TEN

Proportional Report Ratio (PRR) ↓			ESG#
HLGT	HLT	PT	
2.74	3.93	88.26	
10.00	10.00	18.18	
3.00	27.00	82.03	
3.34	4.78	13.29	
2.34	4.00	9.00	
2.25	4.00	12.78	
1.00	12.00	49.40	
10.00	10.00	11450.96	

## Moderately Hard

- Frequency imbalances
- Disproportionality



## Difficult to Identify

- Imbalances only in population subsets
- Interaction with other risk factors



## Examples of a Signal:

- Cases of a designated medical event arising from a spontaneous reporting system,
- Occurrence of a rare adverse event with a near zero background incidence rate,
- An adverse event with a positive dechallenge & rechallenge.

**In order to reliably identify signals:**

**Standardized nomenclature to describe events**

**Application of the nomenclature in a consistent manner**

**Standardized grouping of medically similar terms**

**Standardized methodology for case identification**

## Standardized Nomenclature to Describe Events

- WHOART
- COSTART
- **MedDRA**
- SNOMED

### **Myocardial infarction**

Heart attack

Anterior myocardial infarction

Inferior myocardial infarction

Lateral myocardial infarction

Anteroseptal necrosis

Cardiomyopathy necrotic

## Application of the Nomenclature in a Consistent Manner

- Coding convention rules
  - MedDRA Points to Consider
- Synonym Lists / Coding Thesaurus

**MedDRA<sup>®</sup> TERM SELECTION:  
POINTS TO CONSIDER**

**ICH-Endorsed Guide for MedDRA Users**

## Synonym Lists / Coding Thesaurus

**dsNavigator** Safety in Knowing

Workspace

**AE**

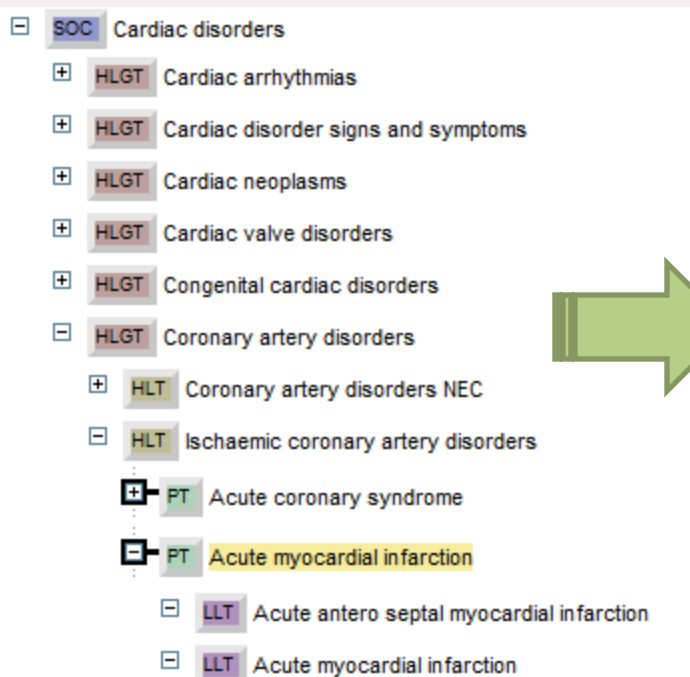
Job Detail **Task Listing** Next Task Export

Tasks 1 to 50 of 56

43	<input type="checkbox"/>		TAXOL REACTION	NEEDS_CODING			Nonspecific reaction
44	<input type="checkbox"/>		WORSENING ELEVATED AST	NEEDS_CODING			AST increased
45	<input type="checkbox"/>		THROMBOCYTOPANIA POST CHEMOTHERAPY	NEEDS_CODING			Nausea post chemotherapy
46	<input type="checkbox"/>		THROMBOCYTOPENIA POST (AFTER) CHEMOTHERAPY	NEEDS_CODING			Nausea post chemotherapy
47	<input type="checkbox"/>		PERIENGRAFTMENT SYNDROME	No Automatch			
48	<input type="checkbox"/>		THORACALGIA	No Automatch			
49	<input type="checkbox"/>		URTICARIA POST PLATELET TRANSFUSION	NEEDS_CODING			Platelet transfusion
50	<input type="checkbox"/>		WORSENING ANEMIA	NEEDS_CODING			Anemia aggravated

## Standardized Grouping of Medically Similar Terms

- MedDRA hierarchical structure



**Table 3.2.3: Adverse Events by System Organ Class**

MedDRA System Organ Class Preferred Term	BLT014 5 mg	Placebo
<b>Cardiac Disorders</b>		
Cardiac arrest	2 (3.4%)	2 (3.1%)
Pericardial effusion	1 (1.7%)	0 (0%)
Sinus tachycardia	5 (8.5%)	1 (1.5%)

## Standardized Methodology for Case Identification

- ❑ Standardized MedDRA Queries (SMQs)
  - Broad
  - Narrow
- ❑ Clinical & Investigations SOC
  - Hyperkalemia + Blood Potassium Decreased
- ❑ Other aggregates of medically similar terms

## SMQ - Narrow

Premalignant disorders (SMQ)		
		<b>Blood premalignant disorders (SMQ)</b>
		<b>Gastrointestinal premalignant disorders (SMQ)</b>
		<b>Premalignant disorders, general conditions and other site specific disorders (SMQ)</b>
		<b>Reproductive premalignant disorders (SMQ)</b>
		<b>Skin premalignant disorders (SMQ)</b>
	Narrow	A Actinic keratosis 10000614
	Narrow	A Arsenical keratosis 10003139
	Narrow	A Dysplastic naevus 10062805
	Narrow	A Dysplastic naevus syndrome 10013960
	Narrow	A Epidermodysplasia verruciformis 10052339
	Narrow	A Erythroplasia 10063121
	Narrow	A Leukoplakia 10062037
	Narrow	A Parapsoriasis 10033898
	Narrow	A Precancerous skin lesion 10049422
	Narrow	A Sebaceous naevus 10039785

## SMQ - Broad

Severe cutaneous adverse reactions (SMQ)			
Narrow	A	Acute generalised exanthematous	10048799
Narrow	A	Cutaneous vasculitis	10011686
Narrow	A	Dermatitis bullous	10012441
Narrow	A	Dermatitis exfoliative	10012455
Narrow	A	Dermatitis exfoliative generalised	10012456
Narrow	A	Epidermal necrosis	10059284
Narrow	A	Erythema multiforme	10015218
Narrow	A	Exfoliative rash	10064579
Narrow	A	Skin necrosis	10040893
Narrow	A	Stevens-Johnson syndrome	10042033
Narrow	A	Toxic epidermal necrolysis	10044223
Narrow	A	Toxic skin eruption	10057970
Broad	A	Acquired epidermolysis bullosa	10056508
Broad	A	Blister	10005191
Broad	A	Bullous impetigo	10006563
Broad	A	Conjunctivitis	10010741
Broad	A	Corneal exfoliation	10064489
Broad	A	Drug eruption	10013687
Broad	A	Drug rash with eosinophilia and sy:	10058919
Broad	A	Epidermolysis	10053177
Broad	A	Epidermolysis bullosa	10014989
Broad	A	Genital ulceration	10018180
Broad	A	Lip exfoliation	10064482
Broad	A	Mouth ulceration	10028034

# Tools in Signal Detection

Event Event Event Event Event Event Event  
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SMQ: Left Ventricular Failure

# Tools in Signal Detection

**Cardiac failure left**

Subject 103-044

<b>AEs</b>	<b>Con Meds</b>
<b>Dyspnea</b>	<b>Doxorubicin</b>
<b>Edema</b>	

Subject 202-031

<b>Chest injury</b>	
<b>Acute renal failure</b>	

Subject 406-002

<b>Dyspnea</b>	
<b>Brain natriuretic peptide increased</b>	

## Clinical & Investigations SOC

Clinical SOC	Preferred Term	Investigations SOC
Metabolism & Nutrition Disorders	Hyperkalemia	Blood potassium increased
Renal & Urinary Disorders	Renal failure	Blood creatinine increased
Blood & Lymphatic System Disorders	Thrombocytopenia	Platelet count decreased

## Other Aggregates of Medically Similar Terms

Medical Concept of Interest	Preferred Terms
Pulmonary toxicity	Dyspnea Cough Wheezing Pleuritis
Fluid retention	Pedal edema Generalized edema Peripheral edema

## Hy's Law Criteria

- >3x ULN elevation of ALT/AST, and
- >2x ULN elevation of total bilirubin, and
- without evidence of cholestasis (alkaline phosphatase <2x ULN), and
- bilirubin elevation at or after time of transaminase elevation, and
- no other etiology (e.g., viral hepatitis)

Guidance for Industry: Drug-Induced Liver Injury – Premarketing Clinical Evaluation

## QTc Prolongation

- ❑ Mean QTc prolongation  $\geq 5$  msec
- ❑ Single cases of absolute QTc duration of  $>450$ ,  $>480$  and  $>500$  msec
- ❑ Single cases of relative QTc increases from baseline of 30 or 60 msec

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Clinical Studies	Post-Marketing
Number of patients with events known	Only know what is spontaneously reported
Number of patients exposed to drug known	Only estimates of the exposed population
Robust ancillary data	Sporadic ancillary data
Sources documents available	Source documents rarely available
Follow-up available	Follow-up rarely available

## Event Rate Calculations

### Clinical Studies

Event Rate

Number of Patients with Event

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Number of Patients Given Drug

### Post-Marketing

Proportional Reporting Rate

Probability of Event with Drug

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Probability of Event with all other Drugs

tsExplorer

Menu Analysis

Analysis Detail

Profile Output History Notes

Signal output: **Hydrocodone analysis**

Signal Output Listing

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Filters New Filter Filter Options

Click on a column's heading to filter its data.

	Item 1 (REACTION: PT)	Item1 SOC	Item1 HLGT	Item1 HLT	Status	RR	OR	PRR	EBGM
1	Nasal necrosis	Respiratory, thoracic and...	Upper respiratory tract d...	Nasal disorders nec		36.631	60.944	60.924	21.693
2	Fear of disease	Psychiatric disorders	Anxiety disorders and sym...	Fear symptoms and phobic ...		21.685	28.274	28.218	20.147
3	Multiple drug overdose ac...	Injury, poisoning and pro...	Medication errors	Overdoses		19.555	24.724	24.679	18.104
4	Cervicobrachial syndrome	Nervous system disorders	Spinal cord and nerve roo...	Cervical spinal cord and ...		19.179	24.100	24.078	16.643
5	Arrhythmia supraventricul...	Cardiac disorders	Cardiac arrhythmias	Supraventricular arrhythm...		16.633	20.252	20.160	16.157
6	Ganglioneuroma	Neoplasms benign, maligna...	Nervous system neoplasms ...	Neuromas		36.964	61.874	61.862	15.744
7	Central venous catheteris...	Surgical and medical proc...	Vascular therapeutic proc...	Venous therapeutic proced...		18.623	23.211	23.198	14.911
8	Occipital neuralgia	Nervous system disorders	Neurological disorders ne...	Sensory abnormalities nec		45.178	89.369	89.356	14.430
9	Facet joint syndrome	Musculoskeletal and conne...	Joint disorders	Joint related disorders n...		21.860	28.527	28.518	14.411

Signal Detection

Signal Graph

**dsExplorer**

Menu :: Event Groups

Analysis

A-B

Drug Mappings

Drug Groups

**Event Groups**

Queries

Duplicate Cases

Signal Detection

Signal Graph

Event Group List

1 to 50 of 1117

	Description	Type
1	SMQ 001 Torsade de pointes/QT prolongation 10.1 (Broad)	SIMPLE
2	SMQ 001 Torsade de pointes/QT prolongation 10.1 (Narrow)	SIMPLE
3	SMQ 001 Torsade de pointes/QT prolongation 12.0 (Broad)	SIMPLE
4	SMQ 001 Torsade de pointes/QT prolongation 12.0 (Narrow)	SIMPLE
5	SMQ 001 Torsade de pointes/QT prolongation 13.0 (Broad)	DICTIONARY
6	SMQ 001 Torsade de pointes/QT prolongation 13.0 (Narrow)	DICTIONARY
7	SMQ 001 Torsade de pointes/QT prolongation 13.1 (Broad)	DICTIONARY
8	SMQ 001 Torsade de pointes/QT prolongation 13.1 (Narrow)	DICTIONARY
9	SMQ 002 Rhabdomyolysis/myopathy 10.1 (Broad)	SIMPLE
10	SMQ 002 Rhabdomyolysis/myopathy 10.1 (Narrow)	SIMPLE
11	SMQ 002 Rhabdomyolysis/myopathy 12.0 (Broad)	SIMPLE
12	SMQ 002 Rhabdomyolysis/myopathy 12.0 (Narrow)	SIMPLE
13	SMQ 002 Rhabdomyolysis/myopathy 13.0 (Broad)	DICTIONARY
14	SMQ 002 Rhabdomyolysis/myopathy 13.0 (Narrow)	DICTIONARY
15	SMQ 002 Rhabdomyolysis/myopathy 13.1 (Broad)	DICTIONARY
16	SMQ 002 Rhabdomyolysis/myopathy 13.1 (Narrow)	DICTIONARY
17	SMQ 003 Acute renal failure 10.1 (Broad)	SIMPLE
18	SMQ 003 Acute renal failure 10.1 (Narrow)	SIMPLE
19	SMQ 003 Acute renal failure 12.0 (Broad)	SIMPLE
20	SMQ 003 Acute renal failure 12.0 (Narrow)	SIMPLE
21	SMQ 003 Acute renal failure 13.0 (Broad)	DICTIONARY
22	SMQ 003 Acute renal failure 13.0 (Narrow)	DICTIONARY

## Framework for a Signal Detection Strategy

### Product Safety Committee

#### Clinical Studies

1. Evaluate serious ICSRs
2. Periodic aggregate assessment of available clinical safety data (DSUR)
3. Evaluate unblinded studies and pooled analyses

#### See also:

- CIOMS VI (Management of Safety Information from Clinical Trials)
- Guidance for Industry: Premarketing Risk Assessment

#### Post-Marketing

1. Evaluate serious ICSRs
2. Periodic aggregate assessment (PSUR)
3. Evaluate events in populations not studied in clinical development
4. Data mining
5. Observational studies/Registries

#### See also:

- Pharmacovigilance Planning ICH E2E
- Vol 9A The Rules Governing Medicinal Products in the European Union