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Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request cder_mpl1r_wp032_nsdp_v01

Request ID: cder_mpl1r_wp032_nsdp_v01.

Query Description: This report contains estimates of the risk of venous thromboembolism (VTE) among new users of combined oral contraceptives (COCs) containing ethinyl estradiol and levonorgestrel.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.3

Data Source: Data from May 22, 2007 to September 30, 2015 from 16 health plans contributing to the Sentinel Distributed Database (SDD) were included in this report. This request was distributed on June 24, 2016. See Appendix A for a list of the latest dates of available data for each Data Partner.

Study Design: This request was a retrospective cohort study. The number of total eligible members, members with the exposure, members with the exposure and the outcome, and member-years at risk were calculated overall and stratified by age group and year.

Exposure of Interest: The exposures of interest were varying types and dosages of COCs containing ethinyl estradiol and levonorgestrel, which were defined using National Drug Codes (NDCs). Please refer to Appendix B for generic and brand names.

Cohort Eligibility Criteria: Patients were required to be continuously enrolled in plans with both medical and drug coverage for at least 6 months (183 days) before their first valid dispensing of the exposure medication, during which gaps in coverage of up to 45 days were allowed. Members were excluded for use of anticoagulants, as listed in Appendix C, or use of COCs containing ethinyl estradiol and levonorgestrel in the 6 months (183 days) prior to exposure initiation. The following age groups were included in the cohort: 18-30, 31-40, 41-50 years. This request was restricted to females.

Follow-Up Time: Follow-up time was determined by the length of the exposure episodes. Exposure episode lengths were defined using the days supply information recorded in outpatient pharmacy dispensings to create a sequence of continuous exposure. Exposure episodes were considered continuous if gaps in days supply were less than 30 days. The end date of each exposure episode was extended by 30 additional days. Follow-up began on the day on which the first exposure of interest was dispensed and continued until the first occurrence of any of the following: 1) the outcome of interest; 2) any codes defining the exposure incidence criteria; 3) disenrollment; 4) the end date of the data provided by each Data Partner; or 5) the end of the exposure episode. The primary analysis examined the first valid episode per person. The sensitivity analysis examined all valid episodes per person.

Outcome of Interest: VTE was defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes, listed in Appendix D. The event was to occur in inpatient care settings.

Please refer to Appendix E for detailed specifications of parameters used in the analyses for this request.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

Sentinel

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Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be

Event Deduplication - specifies how events are counted by the MP algorithm: (0) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1: Summary of the Use of Combined Oral Contraceptives (COC) Containing Ethinyl Estradiol and Levonorgestrel with Outcomes of Venous Thromboembolism (VTE) in the Sentinel Distributed Database (SDD) Between May 22, 2007 and September 30, 2015, by Exposure and Cohort Definition (Females Only)

	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Years at Risk	New Episodes w/ Events	Eligible Members	Member-Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	New Episodes w/ Events/ 10K Years at Risk
Non-Cyclic COCs with Ethinyl Estradiol (20 mcg) and Levonorgestrel (90mcg)														
Retain Only First Valid Episode per Person														
	11,186	11,186	67,071	2,212,447	2,218,506	6,948.7	19	31,049,024	63,529,436.2	0.36	197.79	6.00	32.99	27.34
Retain All Valid Episodes per Person														
	11,186	11,626	69,739	2,301,480	2,307,803	7,230.7	20	31,049,024	63,542,454.5	0.36	205.75	6.23	33.00	27.66
Cyclic COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
	639,898	639,898	3,779,486	153,392,761	152,846,807	467,107.2	375	31,049,805	62,910,099.5	20.61	239.71	5.91	40.59	8.03
Retain All Valid Episodes per Person														
	639,898	697,413	4,032,519	165,186,157	164,624,969	503,702.2	399	31,049,805	63,544,582.6	20.61	258.14	6.30	40.96	7.92
Extended COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
	212,837	212,837	627,915	53,492,159	53,874,631	159,358.2	233.0	31,049,483	63,377,104.6	6.85	251.33	2.95	85.19	14.62
Retain All Valid Episodes per Person														
	212,837	226,176	667,017	56,824,814	57,227,133	169,295.7	248.0	31,049,483	63,543,304.9	6.85	266.99	3.13	85.19	14.65

Table 2: Summary of the Use of Combined Oral Contraceptives (COC) Containing Ethinyl Estradiol and Levonorgestrel with Outcomes of Venous Thromboembolism (VTE) in the Sentinel Distributed Database (SDD) Between May 22, 2007 and September 30, 2015, by Exposure, Cohort Definition, and Age Group (Females Only)

	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Years at Risk	New Episodes w/ Events	Eligible Members	Member-Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	New Episodes w/ Events/ 10K Years at Risk
Non-Cyclic COCs with Ethinyl Estradiol (20 mcg) and Levonorgestrel (90mcg)														
Retain Only First Valid Episode per Person														
18-30 Years	4,623	4,623	24,501	775,825	777,809	2,482.4	4	13,678,394	22,184,860.5	0.34	167.82	5.30	31.67	16.11
31-40 Years	3,966	3,966	24,524	825,542	828,331	2,575.5	10	10,708,011	19,131,785.4	0.37	208.15	6.18	33.66	38.83
41-50 Years	2,597	2,597	18,046	611,080	612,366	1,890.7	5	11,028,380	22,212,790.2	0.24	235.30	6.95	33.86	26.44
Retain All Valid Episodes per Person														
18-30 Years	4,623	4,799	25,359	804,520	806,633	2,575.2	4	13,678,394	22,188,584.1	0.34	174.03	5.49	31.73	15.53
31-40 Years	3,996	4,110	25,550	858,100	860,925	2,678.0	10	10,708,747	19,136,446.1	0.37	214.74	6.39	33.59	37.34
41-50 Years	2,626	2,717	18,830	638,860	640,245	1,977.5	6	11,029,236	22,217,424.3	0.24	243.28	7.17	33.93	30.34
Cyclic COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
18-30 Years	415,824	415,824	2,432,262	97,460,494	96,591,445	297,188.2	140	13,679,001	21,893,604.8	30.40	234.38	5.85	40.07	4.71
31-40 Years	158,859	158,859	926,483	38,553,260	38,663,467	117,376.8	128	10,663,032	18,914,908.1	14.90	242.69	5.83	41.61	10.91
41-50 Years	65,215	65,215	420,741	17,379,007	17,591,896	52,542.2	107	11,002,866	22,101,586.7	5.93	266.49	6.45	41.31	20.36
Retain All Valid Episodes per Person														
18-30 Years	415,824	449,609	2,575,864	104,083,382	103,150,238	317,843.4	147	13,679,001	22,189,940.0	30.40	250.31	6.19	40.41	4.62
31-40 Years	164,400	176,696	1,009,322	42,523,361	42,659,368	129,576.6	141	10,708,953	19,136,991.2	15.35	258.66	6.14	42.13	10.88
41-50 Years	67,270	71,108	447,333	18,579,414	18,815,363	56,282.2	111	11,029,339	22,217,651.4	6.10	276.19	6.65	41.53	19.72
Extended COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
18-30 Years	122,836	122,836	351,924	29,885,140	30,117,934	89,172.2	83	13,678,686	22,117,570.7	8.98	243.29	2.86	84.92	9.31
31-40 Years	61,242	61,242	183,624	15,675,630	15,770,546	46,665.2	76	10,696,256	19,078,322.4	5.73	255.96	3.00	85.37	16.29
41-50 Years	28,759	28,759	92,367	7,931,389	7,986,151	23,520.7	74	11,020,516	22,181,211.5	2.61	275.79	3.21	85.87	31.46
Retain All Valid Episodes per Person														
18-30 Years	122,836	129,652	370,288	31,447,840	31,689,437	93,872.5	94	13,678,686	22,189,070.1	8.98	256.01	3.01	84.93	10.01
31-40 Years	62,497	65,692	197,426	16,850,458	16,952,465	50,143.9	78	10,708,902	19,136,691.4	5.84	269.62	3.16	85.35	15.56
41-50 Years	29,419	30,832	99,303	8,526,516	8,585,231	25,279.2	76	11,029,329	22,217,543.4	2.67	289.83	3.38	85.86	30.06

Table 3: Summary of the Use of Combined Oral Contraceptives (COC) Containing Ethinyl Estradiol and Levonorgestrel with Outcomes of Venous Thromboembolism (VTE) in the Sentinel Distributed Database (SDD) Between May 22, 2007 and September 30, 2015, by Exposure, Cohort Definition, and Year (Females Only)

	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Years at Risk	New Episodes w/ Events	Eligible Members	Member-Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	New Episodes w/ Events/ 10K Years at Risk
Non-Cyclic COCs with Ethinyl Estradiol (20 mcg) and Levonorgestrel (90mcg)														
Retain Only First Valid Episode per Person														
2007	838	838	5,202	172,193	172,315	548.4	0	5,427,315	2,565,600.5	0.15	205.48	6.21	33.10	0.00
2008	3,688	3,688	22,212	724,495	725,437	2,298.1	8	11,445,993	6,744,152.8	0.32	196.45	6.02	32.62	34.81
2009	2,048	2,048	13,614	442,646	443,665	1,379.8	2	11,802,254	8,708,457.4	0.17	216.14	6.65	32.51	14.50
2010	978	978	6,085	211,471	211,970	654.6	3	11,078,452	8,215,369.4	0.09	216.23	6.22	34.75	45.83
2011	904	904	5,376	181,065	181,765	565.5	3	10,623,973	7,915,895.8	0.09	200.29	5.95	33.68	53.05
2012	1,035	1,035	6,728	224,503	225,985	699.5	2	11,070,374	8,028,493.0	0.09	216.91	6.50	33.37	28.59
2013	741	741	4,151	139,182	139,921	433.3	1	11,086,475	8,212,519.3	0.07	187.83	5.60	33.53	23.08
2014	577	577	2,664	87,078	87,408	275.1	0	11,310,286	8,104,230.2	0.05	150.92	4.62	32.69	0.00
2015	377	377	1,039	29,814	30,040	94.5	0	9,617,749	5,034,717.9	0.04	79.08	2.76	28.69	0.00
Retain All Valid Episodes per Person														
2007	838	838	5,202	172,193	172,315	548.4	0	5,427,315	2,565,600.5	0.15	205.48	6.21	33.10	0.00
2008	3,701	3,703	22,280	726,384	727,326	2,304.9	8	11,446,376	6,744,379.9	0.32	196.27	6.02	32.60	34.71
2009	2,122	2,128	14,071	456,837	457,942	1,425.8	3	11,804,251	8,709,728.8	0.18	215.29	6.63	32.47	21.04
2010	1,071	1,072	6,703	233,352	233,981	723.3	3	11,081,166	8,217,362.0	0.10	217.88	6.26	34.81	41.47
2011	978	980	5,853	197,347	198,075	617.1	3	10,626,711	7,918,014.5	0.09	201.79	5.98	33.72	48.61
2012	1,091	1,094	7,124	237,444	238,926	739.8	2	11,073,020	8,030,558.8	0.10	217.64	6.53	33.33	27.03
2013	799	800	4,565	153,165	153,905	476.2	1	11,089,193	8,214,638.5	0.07	191.70	5.71	33.55	21.00
2014	613	614	2,837	92,825	93,175	293.8	0	11,312,946	8,106,264.7	0.05	151.43	4.63	32.72	0.00
2015	397	397	1,104	31,933	32,159	101.3	0	9,619,882	5,035,906.9	0.04	80.44	2.78	28.92	0.00
Cyclic COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
2007	33,900	33,900	208,269	9,154,535	8,776,154	27,876.1	24	5,427,599	2,565,694.6	6.25	270.05	6.14	43.96	8.61
2008	67,121	67,121	439,384	18,183,565	17,980,085	55,246.2	56	11,431,354	6,736,464.3	5.87	270.91	6.55	41.38	10.14
2009	80,947	80,947	544,110	21,881,790	21,804,921	66,438.0	52	11,757,767	8,679,883.8	6.88	270.32	6.72	40.22	7.83
2010	79,191	79,191	531,186	21,715,375	21,611,141	65,818.9	52	11,000,655	8,161,814.2	7.20	274.22	6.71	40.88	7.90
2011	72,898	72,898	466,040	19,379,711	19,335,314	58,865.5	51	10,514,585	7,836,947.6	6.93	265.85	6.39	41.58	8.66
2012	84,935	84,935	555,765	22,293,460	22,276,865	67,625.7	40	10,937,031	7,928,603.4	7.77	262.48	6.54	40.11	5.91
2013	85,528	85,528	509,505	20,274,742	20,305,058	61,758.4	50	10,927,059	8,092,440.3	7.83	237.05	5.96	39.79	8.10
2014	83,785	83,785	389,426	15,394,689	15,510,462	47,477.1	36	11,129,162	7,966,776.0	7.53	183.74	4.65	39.53	7.58
2015	51,593	51,593	135,801	5,114,894	5,246,807	16,001.2	14	9,444,996	4,941,475.4	5.46	99.14	2.63	37.66	8.75
Retain All Valid Episodes per Person														
2007	33,900	33,900	208,269	9,154,535	8,776,154	27,876.1	24	5,427,599	2,565,698.8	6.25	270.05	6.14	43.96	8.61
2008	68,079	68,223	444,403	18,405,719	18,203,633	55,948.6	57	11,446,688	6,744,576.5	5.95	270.36	6.53	41.42	10.19
2009	84,422	84,631	562,135	22,690,895	22,609,187	68,962.6	54	11,804,437	8,709,984.5	7.15	268.78	6.66	40.37	7.83
2010	85,182	85,385	563,021	23,155,640	23,033,945	70,285.0	57	11,081,357	8,217,619.6	7.69	271.84	6.61	41.13	8.11
2011	80,962	81,191	509,162	21,347,347	21,289,143	64,955.2	54	10,626,917	7,918,265.7	7.62	263.67	6.29	41.93	8.31
2012	94,290	94,513	604,782	24,587,298	24,558,760	74,682.7	44	11,073,298	8,030,841.9	8.52	260.76	6.41	40.65	5.89
2013	95,982	96,261	560,512	22,702,644	22,722,863	69,238.4	55	11,089,426	8,214,936.7	8.66	236.53	5.84	40.50	7.94
2014	94,338	94,544	428,580	17,270,088	17,399,991	53,353.4	39	11,313,224	8,106,563.2	8.34	183.07	4.54	40.30	7.31
2015	58,752	58,765	151,655	5,871,991	6,031,292	18,400.2	15	9,620,081	5,036,095.7	6.11	99.95	2.58	38.72	8.15

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	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Years at Risk	New Episodes w/ Events	Eligible Members	Member-Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing	New Episodes w/ Events/ 10K Years at Risk
Extended COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)														
Retain Only First Valid Episode per Person														
2007	8,289	8,289	25,542	2,220,723	2,233,863	6,653.7	8	5,427,423	2,565,628.5	1.53	267.91	3.08	86.94	12.02
2008	21,839	21,839	66,234	5,716,698	5,753,564	17,116.1	29	11,443,443	6,743,091.6	1.91	261.77	3.03	86.31	16.94
2009	32,828	32,828	98,361	8,456,855	8,568,228	25,330.6	42	11,793,150	8,703,580.4	2.78	257.61	3.00	85.98	16.58
2010	34,784	34,784	106,365	9,161,102	9,220,282	27,375.1	46	11,058,819	8,203,456.0	3.15	263.37	3.06	86.13	16.80
2011	32,424	32,424	105,497	9,095,422	9,148,688	27,010.1	35	10,593,227	7,895,675.0	3.06	280.52	3.25	86.21	12.96
2012	25,750	25,750	86,251	7,427,632	7,465,795	21,972.1	28	11,031,630	8,001,850.6	2.33	288.45	3.35	86.12	12.74
2013	22,445	22,445	67,494	5,744,453	5,777,473	17,058.3	19	11,041,545	8,179,920.6	2.03	255.93	3.01	85.11	11.14
2014	21,311	21,311	52,139	4,283,332	4,310,602	12,784.8	20	11,263,681	8,069,858.7	1.89	200.99	2.45	82.15	15.64
2015	13,167	13,167	20,032	1,385,942	1,396,135	4,057.4	6	9,577,906	5,014,043.2	1.37	105.26	1.52	69.19	14.79
Retain All Valid Episodes per Person														
2007	8,289	8,289	25,542	2,220,723	2,233,863	6,653.7	8	5,427,423	2,565,628.7	1.53	267.91	3.08	86.94	12.02
2008	21,977	21,990	66,563	5,745,149	5,782,229	17,204.8	29	11,446,539	6,744,450.2	1.92	261.42	3.03	86.31	16.86
2009	33,549	33,594	100,558	8,646,946	8,759,427	25,904.3	43	11,804,417	8,709,847.5	2.84	257.74	3.00	85.99	16.60
2010	36,435	36,486	111,587	9,616,559	9,678,830	28,744.5	49	11,081,312	8,217,488.3	3.29	263.94	3.06	86.18	17.05
2011	34,929	34,980	114,007	9,832,096	9,889,792	29,200.3	39	10,626,861	7,918,140.4	3.29	281.49	3.26	86.24	13.36
2012	28,293	28,324	95,250	8,207,374	8,249,150	24,277.3	31	11,073,177	8,030,662.6	2.56	290.08	3.37	86.17	12.77
2013	24,654	24,672	74,325	6,329,239	6,365,857	18,801.6	21	11,089,325	8,214,741.6	2.22	256.72	3.01	85.16	11.17
2014	23,408	23,429	57,337	4,712,609	4,742,946	14,071.3	22	11,313,090	8,106,370.5	2.07	201.32	2.45	82.19	15.63
2015	14,412	14,412	21,848	1,514,119	1,525,039	4,437.6	6	9,619,973	5,035,975.2	1.50	105.06	1.52	69.30	13.52

Appendix A: Latest Date of Available Data for Each Data Partner up to Request Date (September 30, 2015)

DP ID	Start Date	End Date
DP0001	1/1/2008	12/31/2014
DP0002	1/1/2006	4/30/2014
DP0003	1/1/2004	10/31/2014
DP0004	1/1/2000	4/30/2012
DP0005	1/1/2000	4/30/2014
DP0006	1/1/2000	2/28/2015
DP0007	1/2/2000	7/31/2012
DP0008	1/2/2000	6/30/2012
DP0009	6/1/2007	10/31/2014
DP0010	1/1/2000	8/31/2014
DP0011	1/1/2000	3/31/2015
DP0012	1/1/2005	3/31/2015
DP0013	1/1/2000	3/31/2015
DP0014	1/2/2000	4/30/2015
DP0015	1/1/2008	12/31/2014
DP0016	1/1/2000	12/31/2012

Appendix B: Generic and Brand Names of Combined Oral Contraceptives (COCs) Used to Define Exposures in this Request

Generic Name	Brand Name
Non-Cyclic COCs with Ethinyl Estradiol (20 mcg) and Levonorgestrel (90mcg)	
LEVONORGESTREL-ETHINYL ESTRADIOL	Lybrel
LEVONORGESTREL-ETHINYL ESTRADIOL	Amethyst
LEVONORGESTREL-ETHINYL ESTRADIOL	levonorgestrel-ethinyl estrad
Cyclic COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)	
LEVONORGESTREL-ETHINYL ESTRADIOL	Tri-Levlen (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Nordette (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Levlen (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Marlissa
LEVONORGESTREL-ETHINYL ESTRADIOL	Levora 0.15/30 (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	Myzilra
LEVONORGESTREL-ETHINYL ESTRADIOL	Trivora (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Levlen (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	Altavera (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Enpresse
LEVONORGESTREL-ETHINYL ESTRADIOL	Chateal
LEVONORGESTREL-ETHINYL ESTRADIOL	Levora-28
LEVONORGESTREL-ETHINYL ESTRADIOL	Levora 0.15/30 (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	levonorgestrel-ethinyl estrad
LEVONORGESTREL-ETHINYL ESTRADIOL	Triphasil (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Triphasil (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	Kurvelo
LEVONORGESTREL-ETHINYL ESTRADIOL	Levonest (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Tri-Levlen (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	Nordette
LEVONORGESTREL-ETHINYL ESTRADIOL	Portia
LEVONORGESTREL-ETHINYL ESTRADIOL	Nordette-21
LEVONORGESTREL-ETHINYL ESTRADIOL	Orsythia
LEVONORGESTREL-ETHINYL ESTRADIOL	Lessina
LEVONORGESTREL-ETHINYL ESTRADIOL	Delyla (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Aubra
LEVONORGESTREL-ETHINYL ESTRADIOL	Alesse (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Lutera (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Sronyx
LEVONORGESTREL-ETHINYL ESTRADIOL	Falmina (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Aviane
LEVONORGESTREL-ETHINYL ESTRADIOL	Levlite (28)
LEVONORGESTREL-ETHINYL ESTRADIOL	Levlite (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	Alesse (21)
LEVONORGESTREL-ETHINYL ESTRADIOL	levonorg-eth estrad triphasic
LEVONORGESTREL-ETHINYL ESTRADIOL	Setlakin
LEVONORGESTREL-ETHINYL ESTRADIOL	Levlen (8)
LEVONORGESTREL-ETHINYL ESTRADIOL	Vienva
Extended COCs with Ethinyl Estradiol (any dose) and Levonorgestrel (any dose)	
LEVONORGESTREL-ETHINYL ESTRADIOL	levonorgestrel-ethinyl estrad
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Amethia Lo
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Camrese
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Daysee
LEVONORGESTREL-ETHINYL ESTRADIOL	Jolessa
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Camrese Lo

Appendix B: Generic and Brand Names of Combined Oral Contraceptives (COCs) Used to Define Exposures in this Request

LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Amethia
LEVONORGESTREL-ETHINYL ESTRADIOL	Introvale
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Quartette
LEVONORGESTREL-ETHINYL ESTRADIOL	Seasonale contraceptive
LEVONORGESTREL-ETHINYL ESTRADIOL	Quasense
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	L norgest/e.estradiol-e.estrad
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	LoSeasonique
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Seasonique
LEVONORGESTREL/ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	Ashlyna

Appendix C: Generic and Brand Names used to Define Anticoagulants in this Request

Generic Name	Brand Name
WARFARIN SODIUM	Warfarin
WARFARIN SODIUM	Coumadin
WARFARIN SODIUM	Jantoven
RIVAROXABAN	Xarelto
APIXABAN	Eliquis
DABIGATRAN ETEXILATE MESYLATE	Pradaxa

Appendix D: List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes Used to Define Venous Thromboembolism (VTE) in this Request

Code	Description
415.1	Pulmonary embolism and infarction
415.1*	Pulmonary embolism and infarction
453	Other venous embolism and thrombosis
453*	Other venous embolism and thrombosis
453**	Other venous embolism and thrombosis

Appendix E: Specifications Document Defining Parameters Used in this Request

The Center for Drug Evaluation and Research (CDER) has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.3, to investigate the risk of venous thromboembolism among new users of cyclic, non-cyclic, and extended combined oral contraceptives. In total, six different scenarios were examined in this request with three different exposures and two different cohort definitions. See below for a description of each of these scenarios.

Enrollment Gap	45 Days
Sex/Age Groups	Females 18-30, 31-40, 41-50 Years
Query Period	May 22, 2007 - September 30, 2015
Coverage Requirement	Medical and Drug Coverage
Enrollment Requirement	183 Days

	Drug/Exposure										Event/Outcome					
Scenario	Incident exposure	Incident w/ respect to:	Episode Truncation at Incident Exposure	Episode Truncation at Death	Washout (days)	Cohort Definition	Episode Gap	Exposure Extension Period	Min Episode Duration	Min Days Supplied	Event/ Outcome	Care Setting/PDX	Incident with Respect to	Incident w/ respect to Care Setting/PDX	Washout (days)	Blackout Period
1	Non-Cyclic Oral Contraceptives with both Ethinyl Estradiol and Levonorgestrel	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain only first episode per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1
2	Cyclic Oral Contraceptives with both Ethinyl Estradiool (any dose) and Levonorgestrel (any dose)	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain only first episode per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1
3	Extended Combined Oral Contraceptives containing Ethinyl Estradiol and Levonorgestrel	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain only first episode per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1
4	Non-Cyclic Oral Contraceptives with both Ethinyl Estradiol and Levonorgestrel	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain all valid episodes per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1
5	Cyclic Oral Contraceptives with both Ethinyl Estradiool (any dose) and Levonorgestrel (any dose)	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain all valid episodes per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1
6	Extended Combined Oral Contraceptives containing Ethinyl Estradiol and Levonorgestrel	All Oral Contraceptive with both Ethinyl Estradiol and Levonorgestrel, Anticoagulants	Yes	No	183	Retain all valid episodes per person	30	30	0	0	Venous Thromboembolism	IP*	Venous Thromboembolism	IP*	183	1

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Provided by Optum360.
Healthcare Common Procedure Coding System (HCPCS) Provided by Optum360.
Current Procedural Terminology, Fourth Edition (CPT-4) Provided by Optum360.
National Drug Codes (NDC) codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus.