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The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

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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Request ID: to16_cap_mpl1r_wp042_nsdp_v01

Report Description: FDA has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) Tool, version 2.0.5, to investigate the estimated number of women aged 10 to 54 years who had multiple births and the number who had both multiple births and a preterm birth during the same encounter.

Methods:

Data Source: The query was run against the Mini-Sentinel Distributed Database (MSDD) for the time period of January 1, 2002 to December 31, 2014. Data from 15 health plans contributing to the MSDD were included in this report.

Study Design: This request was designed to calculate background rates. The rate of multiple births and the rate of both multiple births and a preterm birth during the same encounter in the MSDD were calculated overall and were stratified by year. These rates can be used to estimate the proportion of women with a preterm birth out of the cohort of women with multiple births.

Cohorts of Interest: The two cohorts of interest were 1) women with multiple births and 2) women with multiple births and a preterm birth during the same encounter. Multiple births included liveborn and stillborn births of more than one newborn. Preterm births included deliveries before 37 completed weeks of gestation.

Cohort Eligibility Criteria: Women included in the cohorts were required to be continuously enrolled in plans with both medical and drug coverage for at least 9 months (273 days) before their delivery, during which gaps in coverage of up to 45 days were allowed.

In the first cohort, women were excluded if they had multiple births in the inpatient or emergency department care settings within 9 months (273 days) prior to the multiple births date of interest. All qualifying multiple births that occurred between January 1, 2002 and December 31, 2014 were included.

In the second cohort, women were excluded if they had multiple births and a preterm birth during the same encounter in the inpatient or emergency department care settings within 9 months (273 days) prior to the multiple births date of interest. Women were also excluded from the cohort if they had multiple births in the inpatient or emergency department care settings within 9 months (273 days) prior to the multiple births date of interest. All qualifying encounters with both multiple births and a preterm birth that occurred between January 1, 2002 and December 31, 2014 were included.

Please see Appendix C for a list of parameters used to define the cohorts in this request.

Definitions: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes were used to identify multiple births (please see Appendix A) and preterm births (please see Appendix B).

Notes: Please contact the Mini-Sentinel Operations Center Query Fullfillment Team (production@sentinel.org) for questions and to provide comments/suggestions for future enhancements to this document.

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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 the "RxAmt"

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

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

Censor Episodes at Evidence of Death - indicates whether treatment episodes are truncated based on death date. A member has a death date if he or she has an encounter with a discharge status of "expired" in the Encounter Table, or if he or she has a death date with a

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 dispensings bridged by

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

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

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

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time." (For Intent to Treat analyses only)

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

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

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

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 the occurrence of the incident query code.

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 Women with Multiple Births and Preterm Births in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2002 and December 31, 2012

	Total Number of New Patients in Specified Cohort	Total Number of Incident Births in Specified Cohort	Total Number of Codes	Eligible Members	Member- Years	New Patients / 1K Eligible Members	Number of Codes / Patient
Patients with Multiple Births							
	61,629	62,004	158,058	34,053,831	81,643,616.0	1.81	2.56
Patients with Multiple Births and Preterm Birth during the Same Encounter							
	28,961	29,064	29,064	34,053,831	81,643,616.0	0.85	1.00

Table 2: Summary of Women with Multiple Births and Preterm Births in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2002 and December 31, 2012, by Year

	Total Number of New Patients in Specified Cohort	Total Number of Incident Births in Specified Cohort	Total Number of Codes	Eligible Members	Member- Years	New Patients / 1K Eligible Members	Number of Codes / Patient
Patients with Multiple Births							
2002	1,415	1,415	3,115	2,401,597	1,959,202	0.59	2.20
2003	1,449	1,450	3,222	2,383,899	1,944,405	0.61	2.22
2004	1,477	1,477	3,265	2,536,766	1,989,754	0.58	2.21
2005	1,644	1,644	3,655	2,605,608	2,102,085	0.63	2.22
2006	2,261	2,261	5,339	6,272,718	2,984,494	0.36	2.36
2007	3,997	3,998	9,804	7,025,768	5,474,117	0.57	2.45
2008	5,582	5,582	14,400	14,190,725	7,382,651	0.39	2.58
2009	8,951	8,951	22,916	15,114,757	11,327,772	0.59	2.56
2010	8,472	8,473	21,535	14,222,007	10,806,324	0.60	2.54
2011	7,968	7,968	20,686	13,615,544	10,405,423	0.59	2.60
2012	7,662	7,663	20,075	13,157,579	10,078,347	0.58	2.62
2013	7,064	7,064	18,947	12,493,547	9,537,360	0.57	2.68
2014	4,058	4,058	11,099	10,077,126	5,651,682	0.40	2.74
Patients with Multiple Births and Preterm Birth during the Same Encounter							
2002	675	675	675	2,401,597	1,959,202	0.28	1.00
2003	721	721	721	2,383,899	1,944,405	0.30	1.00
2004	755	755	755	2,536,766	1,989,754	0.30	1.00
2005	825	825	825	2,605,608	2,102,085	0.32	1.00
2006	1,102	1,102	1,102	6,272,718	2,984,494	0.18	1.00
2007	1,936	1,936	1,936	7,025,768	5,474,117	0.28	1.00
2008	2,774	2,774	2,774	14,190,725	7,382,651	0.20	1.00
2009	4,413	4,413	4,413	15,114,757	11,327,772	0.29	1.00
2010	4,046	4,046	4,046	14,222,007	10,806,324	0.28	1.00
2011	3,865	3,865	3,865	13,615,544	10,405,423	0.28	1.00
2012	3,486	3,486	3,486	13,157,579	10,078,347	0.26	1.00
2013	2,918	2,918	2,918	12,493,547	9,537,360	0.23	1.00
2014	1,548	1,548	1,548	10,077,126	5,651,682	0.15	1.00

Code	Description
V31	TWIN BIRTH, MATE LIVEBORN
V31.0	TWIN BIRTH MATE LIVEBORN, BORN IN HOSPITAL
V31.00	TWIN BIRTH MATE LIVEBORN, BORN IN HOSPITAL DELIEVERED WITHOUT MENTION OF CESAREAN
V31.01	TWIN BIRTH MATE LIVEBORN, BORN IN HOSPITAL DELIVERED BY CESAREAN SECTION
V31.1	Twin birth, mate liveborn, born before admission to hospital
V31.2	Twin birth, mate liveborn, born outside hospital and not hospitalized
V32	Twin birth mate stillborn
V32.0	TWIN, BORN IN HOSPITAL, MATE STILLBORN
V32.00	Twin birth mate stillborn born in hospital, delivered without mention of cesarean section
V32.01	TWIN, BORN IN HOSPITAL, CESAREAN, MATE STILLBORN
V32.1	Twin birth, mate stillborn, born before admission to hospital
V32.2	Twin birth, mate stillborn, born outside hospital and not hospitalized
V33	Twin birth unspecified whether mate liveborn or stillborn
V33.0	Twin birth unspecified whether mate liveborn or stillborn born in hospital
V33.00	Twin birth, unspecified whether mate liveborn or stillborn, born in hospital, delivered without mention of cesarean section
V33.01	TWIN, BORN IN HOSPITAL, CESAREAN
V33.1	Twin birth, unspecified whether mate liveborn or stillborn, born before admission to hospital
V33.2	Twin birth, unspecified whether mate liveborn or stillborn, before outside hospital and not hospitalized
V34	Other multiple birth (three or more) mates all liveborn
V34.0	OTHER MULTIPLE, BORN IN HOSPITAL
V34.00	OTHER MULTIPLE, BORN IN HOSPITAL
V34.01	OTHER MULTIPLE, BORN IN HOSPITAL, CESAREAN
V34.1	Other multiple birth (three or more), mates all liveborn, born before admission to hospital
V34.2	Other multiple birth (three or more), mates all liveborn, born outside hospital and not hospitalized
V35	OTHER MULTIPLE, mates stillborn
V35.0	OTHER MULTIPLE, BORN IN HOSPITAL, mates stillborn
V35.00	OTHER MULTIPLE, BORN IN HOSPITAL, mates stillborn
V35.01	OTHER MULTIPLE, BORN IN HOSPITAL, CESAREAN, mates stillborn
V35.1	Other multiple birth (three or more), mates all stillborn, born before admission to hospital
V35.2	Other multiple birth (three or more), mates all stillborn, born outside hospital and not hospitalized

Appendix B: International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes for Preterm Births

Code	Description
765.21	Less than 24 completed weeks of gestation
765.22	24 completed weeks of gestation
765.23	25-26 completed weeks of gestation
765.24	27-28 completed weeks of gestation
765.00	Extreme immaturity
765.01	Extreme immaturity
765.02	Extreme immaturity
765.03	Extreme immaturity
765.04	Extreme immaturity
765.05	Extreme immaturity
765.06	Extreme immaturity
765.07	Extreme immaturity
765.08	Extreme immaturity
765.09	Extreme immaturity
765.25	29-30 completed weeks of gestation
765.26	31-32 completed weeks of gestation
765.27	33-34 completed weeks of gestation
765.28	35-36 completed weeks of gestation
765.10	Other preterm infants
765.11	Other preterm infants
765.12	Other preterm infants
765.13	Other preterm infants
765.14	Other preterm infants
765.15	Other preterm infants
765.16	Other preterm infants
765.17	Other preterm infants
765.18	Other preterm infants
765.19	Other preterm infants
765.20	Preterm with unspecified weeks of gestation
644.21	Onset of delivery before 37 weeks of gestation

Appendix C: Modular Program Specifications for to16_cap_mpl1r_wp042_nsdp_v01

Mini-Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.0.5, was used to determine the number of women with multiple births in the inpatient or emergency department care settings, and to determine the proportion of these women with multiple births and a preterm birth during the same encounter. In total, 2 different scenarios were examined in this report.

Query Period	1/1/2002- 12/31/2014						
Coverage Requirement	Medical and Drug						
Enrollment Requirement	273 days						
Enrollment Gap	45 days						
Age Groups	10-54 (Look at Females Only)						

Drug/Exposure

Run	Incident Exposure	Care Setting	Principal Diagnosis	Incident w/ respect to:	Incident w/ respect to Care Setting	Principal Diagnosis	Washout (days)	Cohort Definition
1	Multiple Births	IP or ED	Any	Multiple Births	IP or ED	Any	273	02
2	Multiple Births and Preterm Birth during same encounter*	IP or ED	Any	Multiple Births and Preterm Birth during same encounter* or Multiple Births alone	IP or ED	Any	273	02

*The date of the Multiple Births code will be used as the exposure date for this conditional set of codes.

ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight