Pregnant and Lactating Persons: Past, Present, and Future

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Abstract

Pregnant and lactating persons represent a substantial U.S. population who may require medications to treat acute or chronic conditions. However, at the time of initial NDA/BLA approval, there are generally no human pregnancy safety or lactation data collected to support the safety of the drug when used during pregnancy or lactation. Purpose: Evaluate FDA's pregnancy and lactation Post Marketing Requirements (PMRs) from the introduction of the FDA Amendments Act (FDAAA) in 2007 to 2020, and to identify past and present trends.

Materials and Methods

Pregnancy and Lactation PMRs were identified from the Postmarketing Requirements and Commitments: Downloadable Database File from the Office of New Drugs. Each PMR was verified using the product approval letter within the Drugs@FDA database. The original NDA/BLA approvals from 2007-2020 were identified using an internal FDA Drug Research and Analysis Host database (DASH). FDA's Document Archiving, Reporting, and Regulatory Tracking Systems (DARRTS) was then used to identify the new division after OND reorganized in early 2020. We excluded drugs that were only approved for use in men, children or postmenopausal women.
Pregnancy PMRs were grouped based on their study design into pregnancy registry, database studies, single-arm/surveillance/pharmacovigilance, pregnancy sub-study in rare disease safety study, and randomized control trial (RCT).
There were also pregnancy PMRs that were issued by the Center for Biologics Evaluation and Research (CBER) (n=18), which were removed as BLAs approved in CBER were not evaluated. The data were analyzed for trends in the number and type of PMRs issued across therapeutic areas and in relation to milestone regulatory events such as public meetings, workshops, and publication of guidance.

Results

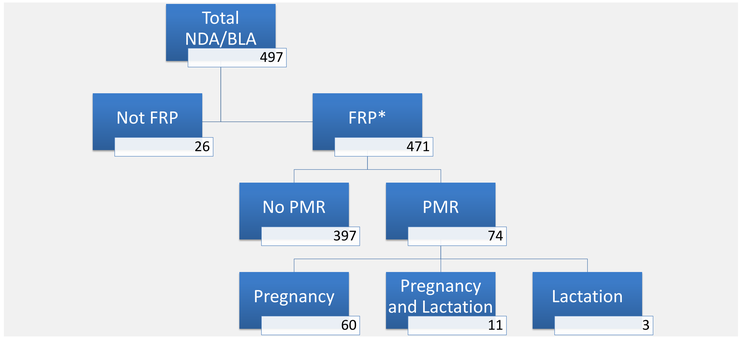

Figure 1. Flowchart of NDA/BLA Approvals and PMRs.
*Females of Reproductive Potential (FRP)

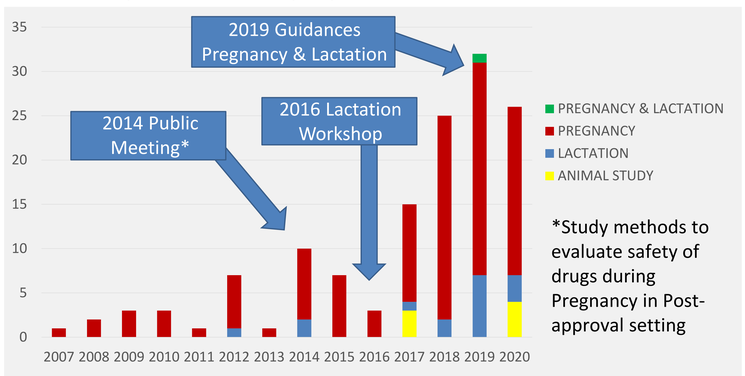

Figure 2. Type of PMR per year

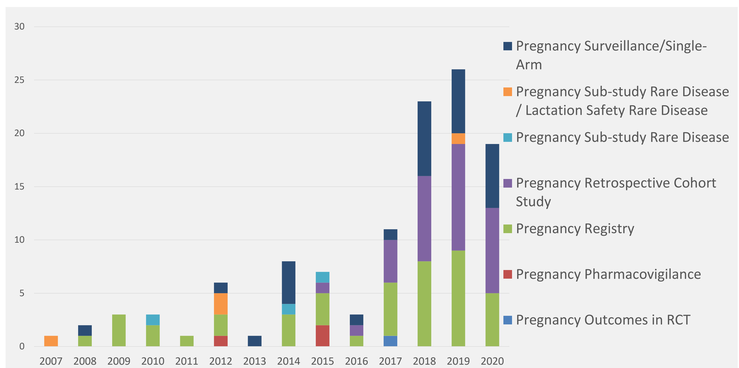

Figure 3. Type of Pregnancy PMR per year

As shown in Figure 2, since the passage of FDAAA (2007-2019), there has been a 13-fold increase in pregnancy PMRs and a 7-fold increase in lactation PMRs. Prior to 2014, there was an average of 3 pregnancy PMRs per year with an increase to 12 in 2014. The largest increase in both pregnancy and lactation PMRs occurred from 2017 to 2019. After 2016, there was also an increase in the number of products that were issued more than one pregnancy PMR with 1 in 2016, 5 in 2017, 4 in 2018, 10 in 2019, and 7 in 2020.

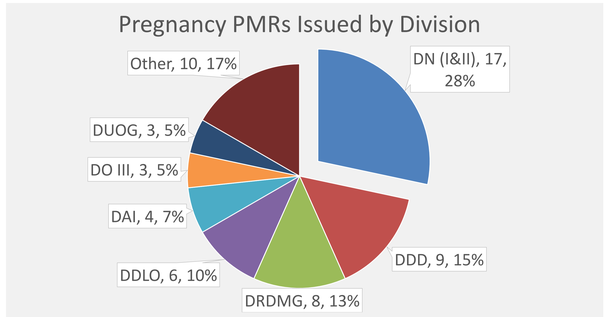

Figure 4. Division issuing Pregnancy PMR
Legend for Figure 4: D = Division. N (I &II) = Neurology I & II, DD = Dermatology and Dentistry, RDMG = Rare Diseases and Medical Genetics, DLO = Diabetes, Lipid Disorders, and Obesity, AI = Anti-infective, O III = Oncology Products III, UOG = Urology, Obstetrics, and Gynecology.
Other = Divisions of Antivirals (n=2, 3%), Non-Malignant Hematology (n=2, 3%), Rheumatology and Transplant Medicine (n=2, 3%), Anesthesiology, Addiction Medicine, and Pain Medicine (n=1, 2%), Cardiology and Nephrology (n=1, 2%), Hematologic Malignancies I (n=1, 2%), Pulmonology, Allergy, and Critical Care (n=1, 2%).

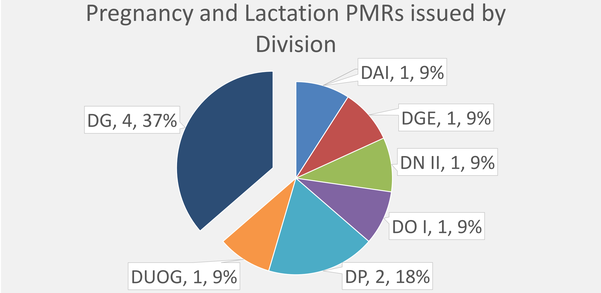

Figure 5. Division issuing both Pregnancy and Lactation PMRs
Legend for Figure 5: D = Division G = Gastroenterology, AI = Anti-infective, GE = General Endocrinology, N = Neurology II, O I = Oncology I, P = Psychiatry, UOG = Urology, Obstetrics, and Gynecology

Pregnancy PMRs (n=60) were most issued for migraine (n=6, 10%), plaque psoriasis (n=6, 10%), and multiple sclerosis (n=6, 10%). Pregnancy and lactation PMRs (n=11) were most issued for chronic idiopathic constipation (n=3, 27%) and sleep disorders (insomnia and narcolepsy) (n=4, 36%).

Discussion

Prior to FDAAA in 2007, Pregnancy and Lactation studies were issued as postmarketing commitments. Since the passage of FDAAA in 2007, there has been an increase in pregnancy and lactation PMRs. However, only 16% of products that may be used in females of reproductive potential were issued pregnancy and/or lactation PMRs. Overall, there appears to be an increase in the number of PMRs issued after 2016. This trend may be related to an increased awareness of the need for these types of studies because of FDA guidances, workshops, and public meetings since 2014. Most PMRs being issued are in conditions common in FRP. However, some drugs that were approved to treat conditions that are common in FRP were not issued a PMR (e.g., obesity, influenza, and type 2 diabetes). We note that a significant proportion of NDA/BLA approvals are for rare diseases or cancers for which certain PMR studies may not be feasible. A limitation of this analysis includes that products such as vaccines approved in the Center for Biologics Evaluation and Research were not evaluated and do not reflect all the pregnancy PMRs that were issued. Future analyses to address this limitation would be helpful.

Conclusion

PMRs are an important regulatory mechanism to obtain safety data in pregnant and lactating persons. Historically, pregnant and lactating persons have been underrepresented in research. With the passage of FDAAA and FDA efforts there has been an increase in PMRs issued in pregnant and lactating persons. However, there is a need for more comprehensive data collection in pregnant and lactating people, as articulated in FDA guidance. Future reviews will hopefully demonstrate improvements in more systematic data collection in pregnant and lactating persons in order to address gaps in knowledge on the safety of medication use in this population.

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