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FDA Public Meeting Report on "Drug Interactions With Hormonal Contraceptives: Public Health and Drug Development Implications"

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Data Sharing

Further inquiries regarding data sharing should be directed to the corresponding author.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Declaration of Conflicting Interests

M.A., E.B-B., D.L.B., M-J.K., L.L., J.A.T., P.E.S., D.G.S., N.K.T., C.Y., and L.Z. are government employees and do not have any financial disclosures. J.H. is an employee and potential stakeholder of Bayer AG. V.S.P. is an employee and potential stakeholder of Pfizer. H.S. is an employee and potential stakeholder of Novartis Institutes for Biomedical Research. All authors wrote and edited this article, and no professional or medical writing company was employed to write this article.

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Abstract

Potential drug interactions with hormonal contraceptives are an important public health concern. A public meeting on "Drug Interactions With Hormonal Contraceptives: Public Health and Drug Development Implication"[1] was hosted by the United States Food and Drug Administration (FDA). The meeting endeavored to provide an opportunity for the FDA to seek input from experts on the public health concerns associated with the use of hormonal contraceptives and interacting drugs that might affect efficacy and safety, including pharmacokinetic/pharmacodynamic considerations, in the design of drug interaction studies of hormonal contraceptives for drug development and approaches to translating the results of drug interaction information into informative labeling and communication. The input received could be used to refine FDA's thinking on hormonal contraceptives drug interaction study design and interpretation and labeling communication of drug interaction risk. This meeting benefited from strong and diverse participation from the Center for Drug Evaluation and Research at the FDA Centers for Disease Control and Prevention, National Institutes of Health, Swedish Medical Products Agency, pharmaceutical industry, and representatives of academia. This report provides a summary of the key discussion based on the presentations and panel discussion.

Keywords

drug interaction; hormonal contraceptive; labeling and communication; drug development

A public meeting entitled "Drug Interactions With Hormonal Contraceptives: Public Health and Drug Development Implications,"[1] co-organized by the Office of Clinical Pharmacology and Office of Women's Health (OWH) of the US Food and Drug Administration (FDA) was held on November 9,2015. The meeting included 3 theme-oriented sessions and a session on research/collaboration opportunities. Sessions I-III had presentations followed by a panel discussion.

- Session I: Hormonal contraceptives and drug interactions in drug development
- Session II: Clinical implications and drug development
- Session III: Clinical practice and communication
- Research/collaboration opportunities

The meeting was opened by Pamela Scott, PhD (FDA, Silver Spring, MD) and David Strauss, MD, PhD (FDA, Silver Spring, MD). They mainly discussed the FDA's mission of protecting and advancing the health of women through development of policy and support for scientific research into products for or used by women. Dr Scott noted that

OWH funded a project to investigate drug-drug interactions (DDIs) involving hormonal contraceptives and that the meeting was organized as a continuation of the FDA's efforts to promote a better understanding of drug interactions that might affect the safety and efficacy of hormonal contraceptives. Dr Strauss, in his opening remarks, stated that unintended pregnancy is a potential adverse outcome in women using hormonal contraceptives if DDIs decrease exposure of hormones. Therefore, investigation of potential drug interactions with hormonal contraceptives, as well as effective communication of known interactions, are important. He outlined many aspects related to DDIs involving hormonal contraceptives in the clinical development of a new drug that need to be considered and highlighted, including questions such as when DDI studies are required, what the most appropriate study design is, whether pharmacodynamic (PD) biomarker endpoints should be considered in study design, how to maximize safety information gathered for relevant interactions, and how to best communicate DDI findings to clinicians and patients.

Alison Edelman, MD, MPH, FACOG (Oregon Health and Science University, Portland, OR) presented a physician's perspective on prescribing hormonal contraceptives to women who have various medical conditions. She provided background on factors that affect the efficacy of contraceptives such as drug adherence, the effect of obesity on the drug's pharmacokinetic (PK) properties, and the understanding of the minimum threshold of exposure for contraceptive efficacy. Based on data from the US Centers for Disease Control and Prevention (CDC),[2] 46.4% of women aged 18–44 years are using at least 1 prescription drug and 11.8% of women are using 3 or more prescription drugs (slide 8 of Supplementary Information 1), therefore, the issue of DDIs is important in the United States. Moreover, it becomes a significant issue for women and healthcare providers when there is a potential for DDIs between hormonal contraceptives and teratogenic drugs. She mentioned that recommendations for the use of hormonal contraceptives can differ between the CDC's Medical Eligibility Criteria and FDA hormonal contraceptives product labeling, therefore, harmonizing different recommendations is warranted.

This report is organized by the key topics of each session (listed above) and highlights the discussion that emerged during the meeting.

Session I: Hormonal Contraceptives and Drug Interactions in Drug Development

This session was organized for presenters to share regulatory and industry perspectives on drug interactions involving hormonal contraceptives. Speakers focused on PK and PD aspects of DDI studies with hormonal contraceptives in drug development, including 1) which concomitant drugs should be investigated in DDI studies with hormonal contraceptives; 2) which key elements need to be considered in designing DDI studies involving hormonal contraceptives; and 3) how study findings can be extrapolated from one specific hormonal contraceptives to other hormonal contraceptives.

Regulatory Perspectives on Clinical Study Endpoint and Data Extrapolation

The presentation of Chongwoo Yu, PhD (FDA, Silver Spring, MD) centered around 2 questions that are important in considering clinical relevance of PK- or PK- and PD-based DDI studies:

- What should be used as the hormonal contraceptives DDI study endpoint: PK only or both PK and PD?
- Can we extrapolate an hormonal contraceptives DDI study result from one progestin/estrogen to another?

In general, PK parameters such as area under the curve (AUC) and peak concentration (C_{max}) are used as the primary endpoints, and the FDA considers no clinically significant drug interaction when 90% CIs for systemic exposure ratios fall entirely within the predefined no-effect boundaries or, if these are not available, within the bioequivalence (BE) limits of 80%−125%.[3] However, there is a challenge in data interpretation for clinically meaningful DDIs when the results are outside of the BE limits. A case example of interpreting PK-based hormonal contraceptives DDI study results (ie, assessing rifampin's effect on dienogest and estradiol valerate PK) outside of the BE limits (eg, an 83% decrease in dienogest exposure and a 44% decrease in estradiol exposure), in which the exposure-response relationship was not fully known, was presented to highlight this challenge (slides 10 and 11 of Supplementary Information 2). A suggested approach for assessing whether the DDI is clinically significant is to explore the feasibility of utilizing PD parameters such as drug-induced alteration in the concentrations of progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Among these, serum progesterone concentration might be useful as a supportive PD DDI indicator in addition to PK data. While it is true that PD assessment has its own caveats of potentially large variability, inconclusive or conflicting data, and the need for a large sample size, it might be useful in the interpretation of DDI study data when the PK results reside outside of the BE limits and no-effect boundaries are not well established.

To address whether a DDI study result can be extrapolated from one progestin/estrogen to another, case examples were presented and discussed. In the first case, 2 studies used the same perpetrator (boceprevir) to evaluate its effect on the PK of different victim combined oral contraceptives containing 2 different progestins (norethindrone and drospirenone) with the same estrogen (ethinyl estradiol [EE]). In the second case, the effect of different perpetrators on the PK of the same combined oral contraceptive regimen was evaluated in 2 different studies; the outcomes for the 2 studies were in conflict (slides 17–21 of Supplementary Information 2). In the first case, boceprevir (ie, perpetrator) caused a 100% increase in drospirenone exposure, while no exposure changes were observed with norethindrone. In the second case, in which the effect of different perpetrators (ie, the strong cytochrome CYP3A inhibitors boceprevir and ketoconazole) on the PK of the same victim combined oral contraceptive was evaluated, there was 24% decrease in EE exposure and a 99% increase in drospirenone exposure with boceprevir and a 40% increase in EE exposure and a 168% increase in drospirenone exposure with ketoconazole. Findings from these cases present the challenge in extrapolating DDI predictions from one to the other combined oral contraceptive based on observed exposure changes, because metabolic

pathways, mechanism of interaction, or extent of contribution from enzymes are potentially different among combined oral contraceptives.

Industry Perspectives on Hormonal Contraceptive DDI Study Design and Data Interpretation

The evaluation of DDI potential with hormonal contraceptives for a new molecular entity (NME) is challenging mainly because of the availability of a wide variety of hormonal contraceptives, as well as their different metabolic profiles and routes of administration. Speakers from 3 pharmaceutical companies provided industry perspectives regarding the assessment during drug development of drug interaction potential with hormonal contraceptives for an NME by presenting their internal guidance or strategies through case examples.

Joachim Höchel, DYM, PhD (Bayer AG, Berlin, Germany) presented the assessment of the drug-interaction potential with hormonal contraceptives for an investigational drug, both as a victim and as a perpetrator. He gave an overview of different in vitro and in vivo assessments for investigational drugs as victim or perpetrator, targeting a mechanistic understanding of the DDI potential, as well as broad population PK-based explorations. He also specifically reviewed the impact of CYP3A inhibitors/CYP3A4 inducers on the PK of hormonal contraceptives such as progestins or estrogens (ie, hormonal contraceptives as the victim drug) to show that the contribution of CYP3A to the elimination is an established common feature of these hormonal contraceptives. For example, strong or moderate CYP3A inhibitors (eg, ketoconazole or erythromycin) increase the exposure of progestins (eg, drospirenone and dienogest) and estrogens (eg, EE and estradiol) whereas CYP3A4 inducers (eg, rifampicin) decrease the exposure of progestins and estrogens (slide 10 of Supplementary Information 3). It was noted that a different DDI magnitude by the CYP3A inhibitors (eg, ketoconazole or erythromycin) was observed with a transdermal hormonal contraceptives product containing EE and gestodene compared with combined oral contraceptives, pointing toward the relative relevance of first-pass versus systemic metabolism (slide 18 of Supplementary Information 3). While there was no change in EE exposure when ketoconazole or erythromycin were given together with the transdermal hormonal contraceptives product, EE exposure increased by 40% when given with a combined oral contraceptive. Transdermal gestodene exposure increased by 23% and 36%, respectively, which was a relatively small change compared with other progestins (dienogest or drospirenone) when given in combined oral contraceptives together with ketoconazole or erythromycin. Dr Höchel also discussed the effects of progestins and estrogens as perpetrators on CYP1A2 and CYP3A substrates (slides 20 and 21 of Supplementary Information 3). He also pointed out that EE caused a 40% increase in the exposure of drospirenone at steady state after multiple-dose coadministration, indicating that the estrogen component affects the elimination pathways of drospirenone, which is not bound to sex hormone-binding globulin (SHBG), so that the known effect of EE on this binding protein cannot be the cause of the observed total drospirenone exposure increase (slide 22 of Supplementary Information 3). In summary, he suggested that DDI potential needs to be assessed in view of the totality of data on the PK/PD relationship regarding efficacy and safety, including consideration of overall variability in the entire population, considering

intrinsic and extrinsic factors. Such assessment of hormonal contraceptives as victims of DDIs is, however, hampered by the fact that their PK/PD relationship is, if at all, known only for ovulation inhibition as one key PD response parameter, but that is not the only factor contributing to contraceptive efficacy. Hence, the relationship between progestin/estrogen concentrations in hormonal contraceptives and contraceptive efficacy is not fully established.

Haiying Sun, PhD (Novartis Institutes for Biomedical Research, East Hanover, NJ) presented the factors to consider for in vivo DDI studies with hormonal contraceptives as victim drugs, as follows: 1) the understanding of in vitro findings such as the relative contribution of metabolic pathways; 2) the results from clinical DDI findings using probe substrate drugs such as midazolam; and 3) the teratogenicity of drugs. She stated that, per the draft DDI guidance issued by the FDA in 2012, clinical DDI studies with hormonal contraceptives for teratogenic NMEs were needed regardless of the findings from in vitro studies. With respect to metabolic pathways of hormonal contraceptives, it is important to understand the contribution of each metabolic pathway to the overall clearance of the hormonal contraceptives components to fully understand potential DDIs involving hormonal contraceptives. Different phase I and II metabolic enzymes, including CYP3A, CYP2C9, CYP2C19, uridine 5’-diphospho-glucuronosyltransferase 1A1, and sulfotransferase 1E1, are responsible for the metabolism of EE and most of the progestins. The investigational drugs that affect these pathways can potentially cause DDIs with hormonal contraceptives. She presented examples that indicated the changes in progestin PK do not always correlate with the potency of CYP3A inhibition, while the extent of PK changes due to CYP3A inhibition for several commonly used progestins, such as norethindrone, levonorgestrel, noregestromin, and 3-ketodesogestrel, are generally small (slide 13 of Supplementary Information 4). She underlined the potential role of SHBG in hormonal contraceptives DDIs especially associated with some progestins, as SHBG can bind progestins. She pointed out that progestin total exposure correlated with SHBG concentrations and time-dependent progestin PK was often observed. Therefore, multiple doses of combined oral contraceptives are often considered for DDI studies (slide 7 of Supplementary Information 4). She also presented her perspective on PD endpoint consideration and mentioned that although the inclusion of PD measurements was not routinely recommended, it might be helpful in some scenarios, for example, if the investigational drug has a relevant PD interaction mechanism that may alter hormone concentrations. Furthermore, as illustrated in the presentation of Dr Yu, PD endpoints may provide supportive information suggesting that efficacy is maintained in spite of observed PK changes (slides 13–15 of Supplementary Information 2). However, there are some challenges in PD data interpretation, including 1) the determination of ovulation is a composite assessment; 2) PD endpoint and sampling points vary among studies; and 3) clinical interpretation of data may differ among investigators. Therefore, currently PK data often drive the conclusion when interpreting oral contraceptive DDI study outcome. For the inclusion of PD data as an endpoint, convincing PD criteria need to be established for meaningful result interpretation.

Vivek Purohit, PhD (Pfizer, Groton, CT) shared Pfizer’s perspective that the need for an oral contraceptive DDI study is always dictated by the properties of the NME, as well as whether the target patient population includes women of childbearing potential who use oral contraceptives. A DDI study with an oral contraceptive should be conducted in

the development program when an NME is a potential teratogen or coadministered with a potential teratogen. In a scenario in which in vitro data obtained from a probe study (eg, with midazolam as a sensitive CYP3A substrate) suggest no CYP3A interaction and a claim of lack of DDIs with oral contraceptives in the label is desired, a confirmatory clinical DDI study is needed. For an NME as an inducer or inhibitor, oral contraceptive DDI studies with probe substrates such as midazolam for CYP3A or other appropriate probe substrates can be conducted. Based on these results, a strategy for oral contraceptive DDIs (ie, oral contraceptive as victim) can be formulated and appropriate labeling language can be written for confirmed results of induction or inhibition. If no oral contraceptive DDI studies are conducted, appropriate labeling language should be considered to caution prescribers and patients about the absence of oral contraceptive DDI studies. Once the need for an oral contraceptive DDI study has been identified, there are several design options that can be considered. For the NME as perpetrator, multiple oral contraceptive dosing can be considered for demonstrating lack of interaction, while a single oral contraceptive dose can be considered if induction or inhibition has been confirmed for the NME using a probe substrate. With respect to study population, healthy women are usually recommended. When PD assessment is important, women of childbearing potential can be considered. DDI studies can be conducted regardless of the women's time of the menstrual cycle if the study is primarily looking to confirm PK interaction because metabolism is not affected by the menstrual cycle, as has been shown for CYP3A. However, if data for PD endpoints are being collected, dosing should be synchronized with the menstrual cycle. In terms of endpoint consideration, PK endpoints such as AUC and C_{max} are adequate to assess DDI potential. Focusing on PK allows simplification of study design, resulting in shorter studies. For PD assessment, FSH, LH, progesterone, and/or ultrasonography can be potential PD endpoints. While there are potential advantages for PD assessments, Dr Purohit suggested they are not recommended routinely because PD endpoints are more variable, and this limits the ability to power a study based on a PD parameter as a primary endpoint. Changes in PD parameters are difficult to detect and take longer to stabilize and, therefore, reach meaningful conclusions.

Session II: Clinical Implications and Drug Development

This session was organized as 3 presentations from the FDA that included discussion of multiple topics related to clinical implications and drug development. Special attention was given to prohibited drugs in phase 3 clinical trials during drug development, drugs with teratogenic potential, and related labeling information.

Myong-Jin Kim, PharmD (FDA, Silver Spring, MD) presented on prohibited drugs in phase 3 clinical trials during hormonal contraceptives drug development and reported that phase 3 trials often exclude relevant concomitant drugs that might affect the efficacy or safety of the investigational hormonal contraceptives. In this regard, large numbers of various drugs have been excluded, including anticoagulants, antiepileptics, hypnotics and sedatives, continuous systemic antibiotics, and products containing St. John's wort. She stated that FDA-approved non-oral hormonal contraceptives products, including vaginal rings, intrauterine systems, and implants, have also excluded these medications in their phase 3 trials. In her presentation, she outlined the labeling of non-oral hormonal contraceptives

products, such as intramuscular injections, transdermal patches, vaginal rings, intrauterine systems, and implants, and reported that hormonal contraceptives product labeling has standard labeling language on drug interaction regardless of administration route.

Melissa S. Tassinari, PhD, DABT (FDA, Silver Spring, MD) pointed out in her presentation that evidence from nonclinical studies, such as reproductive and developmental toxicity studies, should be considered during drug development to predict the teratogenic potential of an NME. These toxicity studies are conducted as 1 of 3 approaches: fertility and early embryonic development study, embryonic/fetal development study, or pre- and postnatal development study. These studies are specifically designed to assess the full range of potential adverse issues. The characteristics of the drug itself, or its drug class, and the impact of maternal disease or condition on pregnancy outcome also need to be considered to estimate teratogenic potential. A teratogen is a substance or agent that interferes with normal prenatal development, causing the formation of developmental abnormalities of the embryo or fetus. When women of reproductive potential need to take teratogenic medications, prevention of pregnancy is critical for mitigating the risk for teratogenicity. Because they need to be coadministered, the DDI potential should be evaluated to ensure the safe and effective use of hormonal contraceptives. Dr Tassinari also noted that whether a drug is a teratogen depends on the dosage regimen, route of administration, and duration and timing of exposure during pregnancy. If there is any teratogenic potential identified or suspected, clinical DDI studies for hormonal contraceptives should be conducted. Recommendations for contraceptive methods in large-scale trials during drug development and, subsequently, for approved labeling should be informed from these clinical hormonal contraceptives DDI study outcomes and any other data pertinent to such decisions.

Li Li, PhD (FDA, Silver Spring, MD) summarized her survey, aimed at understanding the current practice of conducting clinical DDI studies of systemically acting hormonal contraceptives and potentially teratogenic drugs, and to understand the current practice of applying available DDI data to the choice of reliable contraceptive methods in clinical trials and to enhance product labeling. Conducting DDI studies of hormonal contraceptives and drugs with teratogenic potential has not been a common practice and it was found that 17% of 18 drugs with teratogenic potential had no contraceptive information in their labeling (Slide 10 of Supplementary Information 8). Moreover, hormonal contraceptives were sometimes allowed to be used in phase 3 clinical studies without ruling out enzyme induction potential by conducting clinical DDI studies prior to phase 3 clinical studies, which might decrease contraceptive effectiveness. For product labeling, DDI studies of hormonal contraceptives are reflected in their labeling, however, instruction on effective contraception varies. She commented that clinical DDI evaluation with hormonal contraceptives is important for providing evidence-based guidance on reliable contraceptive methods for female patients to effectively mitigate the risk for teratogenicity as a result of unintended pregnancy.

Session III: Clinical Practice and Communication

In this session, speakers from CDC and academic institutions presented information on clinical guidance, product labeling, and effective communication, focusing on how the

clinical utility of hormonal contraceptives DDI information in FDA-approved labeling can be improved in a concise and comprehensible manner.

Naomi Tepper, MD, MPH, FACOG (CDC, Atlanta, GA) presented an overview of CDC's contraceptive guidance. Certain potential drug interactions with hormonal contraceptives are addressed in the US medical eligibility criteria, which provides recommendations for the safe use of contraceptive methods by women with certain medical conditions, such as hypertension, diabetes, and HIV.[4] The US medical eligibility criteria includes recommendations for women using certain medications, including antiretrovirals, anticonvulsants, antimicrobials, psychotropic medications, and St. John's wort (the latter 2 drug categories were not yet included in the US medical eligibility criteria at the time of the meeting; Slide 12 of Supplementary Information 9). A variety of US medical eligibility criteria tools are available for healthcare providers online at no cost, including summary charts, US medical eligibility criteria wheel, and a mobile app.

Erin Berry-Bibee, MD, MPH (CDC, Atlanta, GA) discussed the process of generating recommendations for the US medical eligibility criteria, focusing on the guidelines for drug interactions. The process used by CDC to generate these recommendations include the following steps: 1) identifying areas of scientific or clinical concern; 2) conducting systematic reviews; 3) presenting evidence to family planning experts and other key stakeholders; 4) collecting individual input from these participants on how the evidence might translate into recommendations; and 5) generating clinical recommendations. However, there are some challenges in translating the evidence on drug interactions into clinical guidance, such as lack of evidence on clinical outcomes, identifying the PD outcomes that are best to consider, and determining how PK data can be translated into clinical recommendations that accurately reflect theoretical or proven concerns.

From the perspective of a practicing clinician, it can be difficult to prescribe hormonal contraceptives for patients with uncommon comorbidities or using unfamiliar medications because of a lack of appropriate DDI information. Roxanne Jamshidi, MD, MPH, FACOG (George Washington University, Washington, DC) stated that many clinicians do not look at product labeling because the labeling lacks up-to-date, evidence-based information. In such situations, clinicians first look at the US medical eligibility criteria, which is easy to read and is evidence based. Other resources are also available, such as Micromedex, Up To Date, DynaMed, www.hiv-druginteraction.org, and Aidsinfo.nih.gov (Slide 5 of Supplementary Information 11). It was suggested that product labeling be more informative so that non-obstetricians/-gynecologists, who may not regularly prescribe hormonal contraceptives, will use product labeling to find the necessary information.

Ruth Day, PhD (Duke University, Durham, NC) discussed how appropriate DDI information can be provided in prescribing information, yet be hard to find, understand, remember, and use. Alternative displays of key information, such as schematic tables and figures, can increase the "cognitive accessibility"[5] of the information. These displays can be useful in several sections of labeling, including drug interactions, clinical pharmacology, and dosage and administration, as well as patient counseling. They can replace chunks of traditional text or supplement it. Because spatial displays enhance key information (such as the main drugs

that pose an interaction risk), they can serve as a “wall chart”—people can understand the information quickly and glance back at it later as a reminder.

Summary of the Panel Discussion

Drug Development Perspective—In the panel discussion on topics related to session I, panel members centered their discussion on the following questions and discussion points:

- **a.** During hormonal contraceptives drug development, how do you decide which concomitant drugs to study in the DDI study?
- **b.** Which key elements need to be considered in hormonal contraceptives DDI study design, including population (pre- and postmenopausal women, healthy women, and/or women with medical conditions), endpoints (PK, PD, or both, and which outcome), choice and dose of hormonal contraceptives, and study duration?
- **c.** What are the major challenges in relying on dedicated hormonal contraceptives DDI study results to make recommendations on hormonal contraceptives use in the intended patient populations, including extrapolating the study findings of one specific hormonal contraceptives to other hormonal contraceptives and interpretation of PK and/or PD results?
- **d.** What other data and methodologies besides a dedicated study can help in clinical decision making and recommendations?

Several key issues were discussed by the panel members. First, for the development of new hormonal contraceptives, the following are needed: complete quantitative information about the disposition pathways of the drug; efficacy and safety data from dose-ranging studies; exposure-response relationship; and an in vitro profile of the drug that elucidates whether it is a substrate for transporter or substrate for the CYP, uridine 5’-diphospho-glucuronosyltransferase, or sulfotransferase enzymes, so that development follows the same guidelines as established for other NMEs. Regarding the choice of combined oral contraceptive for DDI studies with an NME as perpetrator, it was recommended that the most commonly used combined oral contraceptive be selected to maximize the benefit of the study and provide clinically relevant information. It should be noted that extrapolation of DDI results for one combined oral contraceptive to another may not be reliable due to differences in metabolism/transport pathways of components of the various combined oral contraceptives. Second, in the drug development process, consideration of study subjects who ultimately will use the drug (eg, whether it is pre- or postmenopausal women) is important because menstrual cycle may affect the outcome, particularly for acute treatment, although for chronic treatments it may not be a big issue. Usually, DDI studies are conducted in healthy subjects who are not taking concomitant medications. However, patients taking hormonal contraceptives might be obese or on various concomitant medications and this should be considered when designing DDI studies involving hormonal contraceptives. It was stated that LH and FSH as PD endpoints are unreliable, as they need to be measured too frequently. In addition, the outcome is subject to when the sample is collected, as LH and FSH have a narrow window of surge at mid-cycle and can shift depending on how each individual uses the contraceptives. In contrast, progesterone

concentrations may be useful when measured at 2- or 3-day intervals to avoid missing an ovulatory rise in progesterone. Third, panel members said that one of the challenges is determining which PK parameter (eg, AUC, C_{max}, or trough concentration) to consider for contraceptive efficacy for assessment of hormonal contraceptives DDI potential. Based on modeling analysis, it was suggested that AUC should be utilized for efficacy considerations for consistent hormonal contraceptives users and trough concentration for inconsistent hormonal contraceptives users. It is difficult to determine the minimum threshold for efficacy, as most hormonal contraceptives do not have a specific value associated with minimum ovulatory suppression. This makes it very difficult for clinicians to utilize PK data to assess the impact on efficacy. Therefore, it was suggested by some panelists that PD values might aid in better understanding exposure-response or dose-response relationships and in making clinical recommendations. In terms of extrapolating the study findings of one specific hormonal contraceptives to another hormonal contraceptives, panel members mentioned that extrapolation may be made based on the shared understanding of hormonal contraceptives' metabolic pathways. In addition, panel members mentioned that the inclusion in clinical trials of patients who are obese may help clinicians make clinical decisions and recommendations, as there is an impact of body mass index (BMI) or body weight on the PK of hormonal contraceptives.[6] A population PK/PD analysis of the impact of different factors, such as body weight, on exposure and a correlation analysis with PD would be helpful in making better determinations of which effects are clinically relevant.

Clinical Implications and Drug Development—The session II panel discussion addressed the following questions and discussion topics:

- **a.** Exclusion of relevant concomitant drugs in phase 3 trials of hormonal contraceptives.
  - **i.** Discuss how to maximize the safety information gathered (and, in turn, labeling implications) for relevant DDIs while ethically ensuring the trial does not significantly elevate risks for the subjects (ie, determining which concomitant drugs to allow in trials).
  - **ii.** Comment on the extent to which concerns about impaired efficacy in the face of potential DDIs also drive the exclusion of concomitant medications in phase 3 trials. Provide suggestions on how this can be addressed to obtain a good "real world" view of how the drug performs in the face of concomitant medication use.
- **b.** Should hormonal contraceptives DDI be evaluated for all drugs with females of reproductive potential (FRP) as part of the intended patient population? Also comment on teratogens in FRP.
  - **i.** What are the major considerations in determining the need and strategy to address hormonal contraceptives DDI during drug development?
  - **ii.** What level of DDI evidence leads to instructing women to use backup contraception when the interacting drug is used (both in clinical trial

instructions and in labeling)? What evidence supports statements on how long the backup method should be used?

c. Non-oral hormonal contraceptives have standard language on drug interactions regardless of their route of administration. Comment on any unique aspects to consider for these non-oral hormonal contraceptives and their drug interaction potentials.

During the discussion, panel members were asked what the major considerations are in determining the need and strategy for addressing hormonal contraceptives DDIs during drug development. Panel members responded that conducting DDI studies before phase 3 trials (eg, sometime around the start of phase 2 studies) is important for assisting in the recruitment and retention of subjects in the trial, as it will help avoid unintended pregnancies. One panelist mentioned that before women of childbearing potential are enrolled into the studies, it is important to assess drug interaction potential based on the available data, eg, in vitro phenotyping and whether the drug is an inducer or not. Teratogens should not be permitted or the study can be restricted to women who do not use hormonal contraceptives if there are no clinical drug interaction data available. There were also discussions regarding effective contraception and what level of DDI evidence leads to instructing women to use backup contraception when the interacting drug is used; when an interaction may potentially reduce hormonal contraceptives efficacy, labeling should make that clear and understandable to the clinician. Moreover, duration of the backup method is also an important concern and it was suggested that it should be based on half-lives of the drug. It was suggested that epidemiological information might help to address this issue. In some cases, such as with antiretroviral drugs, women receive lifelong treatment and it is ideal to recommend long-term dual protection with effective contraception and a barrier method.

Non-oral hormonal contraceptives have the same standard labeling language as oral contraceptives regardless of their route of administration. It was asked whether there were comments regarding unique aspects to consider for these non-oral hormonal contraceptives and their drug interaction potentials. It was suggested that for non-oral hormonal contraceptives, systemically acting formulations should be differentiated from primarily locally acting formulations for consideration of DDIs, and that data from phase 2 and 3 trials and all other available information should be used to make a comprehensive decision regarding hormonal contraceptives labeling.

Clinical Practice and Communication Perspective—The session III panel discussion was devoted to different aspects of labeling recommendations on hormonal contraceptives DDIs and how the clinical utility of labeling, from the physician's perspective, can be improved. The panel discussion was based on the following questions or topics:

a. Due to the significant public health implications, how do we reconcile differing clinical recommendations between the FDA-approved labeling and clinical practice guidelines such as CDC's US medical eligibility criteria?

b. Are there general recommendations that would improve the clinical utility of hormonal contraceptives DDI information in FDA-approved labeling (ie, what do healthcare providers want to see)?

c. What practical labeling recommendations can be made regarding alternative methods of birth control when significant interactions or teratogenic concerns exist (eg, alternatives to double barrier methods)?

A discussion took place regarding the differences between FDA-approved labeling and clinical practice guidelines. For example, the US medical eligibility criteria comprises broader recommendations on contraceptive safety, efficacy, and provision, based on systemic reviews of the published data, while FDA labeling has a narrow focus on the data supporting safety and efficacy in the new drug application submitted by the company to the FDA. In response, an FDA representative clarified that FDA labeling recommendations are also based on published literature. However, the FDA relies on the drug developer to submit such information for its consideration and may request the drug developer submit a labeling supplement if a need is found based on the provided literature.

Regarding recommendations whether or not to use hormonal contraceptives because of potential DDIs, it was mentioned that, as some of this is a "gray area," risk and benefit language (eg, weighing risks and benefits, including consideration of the risk for compromised hormonal contraceptives efficacy vs other methods of contraception) would be useful to healthcare providers. For providers concerned about the effectiveness of hormonal contraceptives, the alternative would be to recommend use of a condom or copper intrauterine device, however, such methods may not be universally available. Therefore, caution should be made in using statements such as "do not use this method" or "do not use this particular contraceptive product" because such statements can be counterproductive.

In terms of improving the clinical utility of hormonal contraceptives DDI information in FDA labeling, panel members were not sure whether forest plots are the most effective way to convey DDI information. Panel members said that labeling information needs to be as detailed as possible, including actual DDI study information or whether it has been extrapolated from a different hormonal contraceptives. Moreover, the potential effect of DDIs should be expressed in clear language. The physician labeling rule format improved communication via labeling, however, to make labeling information simpler and easier to access, read, and understand, it was suggested that key information be represented in spatial displays such as tables, pictures, or figures, including forest plots. It should be noted that the FDA recently published its draft guidance for industry entitled "Labeling for Combined Hormonal Contraceptives."[7] This draft guidance provides recommendations on information that should be included in the prescribing information for combined hormonal contraceptives that contain estrogen and progestin. Combined hormonal contraceptives include combined oral contraceptives, as well as non-oral products such as transdermal systems and vaginal rings. Many of the labeling recommendations in this draft guidance represent class labeling that should be included in all combined hormonal contraceptives prescribing information.

Concluding Session: Research and Collaboration Opportunity

The FDA mission is not only to protect public health but also to advance public health by stimulating and driving innovation and modernizing drug development and regulatory review. In this session, ongoing research collaborations conducted by different agencies and possible future research opportunities were discussed by the presenters.

Jim A. Turpin, PhD (National Institutes of Health [NIH], Bethesda, MD) discussed collaborative research with the National Institute of Allergy and Infectious Diseases, CDC, FDA, and other funders such as the Bill and Melinda Gates Foundation. He reported that National Institute of Allergy and Infectious Diseases-funded activities are laying the groundwork for developing an understanding of the interaction of endogenous and exogenous hormones with the female genital tract in the context of susceptibility to HIV infection. He also mentioned the development of multipurpose prevention strategies, composed of a contraceptive coformulated or coadministered with antivirals or other drugs, to inhibit sexually transmitted infections and the potential role of DDIs in this context (Slide 9 of Supplementary Information 13).

Diana Blithe, PhD (NIH, Bethesda, MD) presented the effect of obesity or BMI on contraceptive efficacy and mentioned that a study of a contraceptive patch containing norelgestromin and EE showed that there were 15 pregnancies in 3319 women and that the failures were clustered in the women who had greater weight (Slide 8 of Supplementary Information 14). FDA did a meta-analysis of 7 combined oral contraceptives containing different progestins (of different doses) and found a significant effect of obesity on drug effectiveness.[6] Dr Blithe also showed results from studies of levonorgestrel contraceptive methods that noted an effect of body weight on contraceptive efficacy (Slide 11 of Supplementary Information 14).

Lei Zhang, PhD (FDA, Silver Spring, MD) mentioned that it is important to identify the key considerations for study designs and maximize the knowledge gained for decision making, as it is not practical to conduct every possible DDI study. She emphasized the need to develop models of different metabolic and transport pathways to extrapolate to unstudied interactions, especially for the progestin components of combined oral contraceptives, and to understand their exposure-response relationships to translate the PK observation into PD or clinical outcome. The development of validated physiologically based PK models to understand DDIs in any unstudied scenario can be a good tool for addressing hormonal contraceptives DDI potentials. The importance of enhancing labeling and health communications were also discussed. Moreover, there are some disease conditions, for example, HIV susceptibility, that may warrant more research to understand the risks and benefits of hormonal contraceptives use in a particular patient population. She stated that collaboration is critical for working with the larger scientific community on developing solutions to critical questions and challenges; to that end, FDA has research collaborations with NIH and other entities.

Future Perspectives

In this meeting, speakers from federal agencies, industry, and academia discussed important issues related to drug interactions between hormonal contraceptives and concomitant medications. The discussions included, for example, what minimum threshold should be used to define a clinically meaningful impact on efficacy, and whether evaluating PK alone is sufficient or whether a PK/PD-based drug interaction study approach is needed. Participants largely agreed on certain issues, for example, interpretation of data from PK-only DDI studies is more straightforward than from PD studies, and data extrapolation from one hormonal contraceptives DDI study to another is challenging. However, further research and discussion are warranted to aid the safe and effective use of hormonal contraceptives, especially when the DDI is expected with concomitant medications that are commonly used in the hormonal contraceptives target population. It was suggested that understanding drug interaction potential of NMEs and hormonal contraceptives is important in the design and conduct of clinical trials. Greater knowledge of drug interaction mechanisms will lead to new insights in the clinical investigation of drug interactions with hormonal contraceptives. It was reported that conducting DDI studies of hormonal contraceptives and drugs with teratogenic potential is not a common practice. In the case of women who have been exposed to drugs with the potential to cause birth defects, both women and their healthcare providers need more information about potential interactions to determine the risks to the individual patient.

Clinicians need specific and clear information in drug labeling so they can accurately instruct women on the appropriate course of action. Moreover, healthcare providers need evidence-based, specific, and concise information to guide their decisions. Therefore, it was recommended that the clinical usefulness of drug interaction information in FDA-approved labeling for hormonal contraceptives be improved. It was reported that the clinical usefulness, or even applicability, of drug interaction labeling for non-oral and/or non-systemically acting hormonal contraceptives (eg, intrauterine devices) is unclear, because they are labeled with the same information as combined oral contraceptives, but would potentially demonstrate different DDI effects if studied. These differences need to be addressed in the labeling. However, as there are no available data, the FDA can only warn that the potential combined oral contraceptive DDI data may not be generalizable to contraceptives with a different route of administration. The efficacy of hormonal contraceptives can be impaired by higher body weight or BMI, and it was suggested that more guidance in labeling on recommended course of action be required. Overall, this meeting allowed the unique opportunity for representatives from federal agencies, industry, and academia to identify the critical knowledge gaps, areas needing further research, and research opportunities in hormonal contraceptives DDI studies to ensure the safe use of hormonal contraceptives and appropriate clinical communication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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